Digitized by the Internet Archive
in 2013

http://archive.org/details/transactionsstud4719coll

TRANSACTIONS & STUDIES

of the

College of Physicians

of

Philadelphia

FOURTH SERIES

VOLUME 7

1939-40

WAVERLY PRESS, INC.

Baltimore, Md.

Views expressed by contributors to the *Transactions & Studies of the College of Physicians of Philadelphia* are to be understood as not necessarily reflecting those held by the College.

Contents

NO. 1, APRIL, 1939

Studies Pertaining to the Origin and Nature of Hypertrophic Arthritis . . . . . *Walter Bauer* 1
Diabetes Mellitus in the Light of Our Present Knowledge of Metabolism . . . . . *C. N. H. Long* 21
Section on General Medicine: Programs and Abstracts (including reports on the use of sulfapyridine) 47
Section on Medical History: Program and Abstracts 57
Sections on Ophthalmology, Otolaryngology, and Public Health, Preventive and Industrial Medicine: Programs 61
Currents and Counter-currents in the Progress of Medicine *Alfred Stengel* 64
Clinical Teaching in America, with Some Remarks on Early Medical Schools . . . . . *David Riesman* 89

Memoirs

John H. Girvin . . . . . *Francis R. Packard* 111
Lawrence F. Flick . . . . . *Joseph Walsh* 114
Michael Burns . . . . . *Edward A. Strecker* 120
College Notes 121
Officers and Committees, 1939 124

NO. 2, JUNE, 1939

The Diagnosis and Treatment of Anemia . . . . *W. B. Castle* 129
A New Approach to the Etiology and Treatment of Angina Pectoris *William J. Kerr* 162
The College: Programs 171
Sections on General Medicine, Medical History, Ophthalmology, Otolaryngology, and Public Health, Preventive and Industrial Medicine: Programs 171
Preventive Medicine in the Bible and Talmud *Maurice S. Jacobs* 175
Karl Sudhoff, 1853–1938 . . . . . *Edward B. Krumbhaar* 189

Memoirs

Addinell Hewson . . . . . *J. Parsons Schaeffer* 192
Benjamin Franklin Baer, Jr. . . . . *George Morris Piersol* 198
College Notes 205

NO. 3. DECEMBER, 1939

The Surgical Approach to Diseases of the Heart . *Claude S. Beck* 211
The Rickettsioses of North America . . . . . *R. E. Dyer* 232
Section on General Medicine: Program and Abstracts 260
Sections on Medical History, Ophthalmology, Otolaryngology, and Public Health, Preventive and Industrial Medicine: Programs 262
The Legacy of Rome in the History of Medicine *Arturo Castiglioni* 264
A Resurrection of "Pile": the Peter A. Browne Collection of Hair in the Mütter Museum . . . . . *Joseph McFarland* 278
College Notes 297

NO. 4, FEBRUARY, 1940

Certain Ovarian Tumors Associated with Sexual Endocrine Dysfunction . . . . . *Howard T. Karsner* 301
Experiments in the Environmental Control of Epidemic Respiratory Infection . . . . . *W. F. Wells, Joseph Stokes, Jr., Mildred W. Wells, and Theodore S. Wilder* 342
Transactions of the College (*Authors and Titles*), 1939 345
Section on General Medicine: Programs and Abstracts 347
Sections on Medical History, Ophthalmology, Otolaryngology, and Public Health, Preventive and Industrial Medicine: Programs 350
The Medico-Mnemonic Treatise (1491) of Johannes Michael Albertus Carrariensis . . . . . *W. B. McDaniel, 2d* 353

Annual Reports

The President's Address . . . . . *George P. Muller* 369
Library Committee, 381; Committee on the Mütter Museum, 396; Committee on College Collections, 398; Treasurer, 399; Women's Committee on the Sinkler Garden, 405
Index to Volume 7 407

Studies Pertaining to the Origin and Nature of Hypertrophic Arthritis†*[1,2]

By Walter Bauer, M.D.

Associate Professor and Tutor in Medicine, Harvard Medical School

One of the principal factors responsible for the increasing attention given to arthritis in this country can be traced directly to Philadelphia. Due largely to the efforts of one of your Fellows, Dr. Ralph Pemberton, these socially and economically important diseases are beginning to receive the study they merit. He has made this possible through the creation of the American Committee for the Prevention and Control of Rheumatism and its direct descendant, The American Rheumatism Society. Therefore, it seems most fitting that one of the 1939 Nathan Lewis Hatfield lectures should be devoted to the subject of arthritis. I greatly appreciate the honor of having been invited to give it.

Much that one reads pertaining to hypertrophic arthritis is confusing and contradictory. To begin with, there exists no universally-adopted nomenclature. Many physicians, particularly the roentgenologists, prefer the term, hypertrophic arthritis, yet others employ the terms, osteo-arthritis, degenerative arthritis, menopausal or climacteric arthritis, senescent or senile arthritis, osteoarthrosis, arthritis deformans and degenerative joint disease, to signify the existence of the same disease process. From this varied terminology alone one might rightly conclude

† Nathan Lewis Hatfield Lecture XXI, College of Physicians of Philadelphia, January 4, 1939.

* This is publication No. 28 of the Robert W. Lovett Memorial for the study of crippling disease, Harvard Medical School, Boston, Mass.

[1] From the Medical Clinic of the Massachusetts General Hospital, the Department of Medicine, Harvard Medical School, Boston, and the Massachusetts Department of Public Health.

[2] The expenses of this investigation have been defrayed by a grant from the Commonwealth Fund.

that there exists no uniformity of opinion concerning the exact nature of this type of joint disease. Consideration of the various etiological theories is equally confusing. Although most workers are agreed that trauma plays a major rôle in the production of hypertrophic arthritis, others consider it to be the result of some type of metabolic disorder, dysfunction of one or more of the endocrine glands, circulatory disturbances, physiological aging, various infectious agents and toxins. To add further to the confusion, certain workers consider hypertrophic arthritis and rheumatoid arthritis varied manifestations of the same disease.

Such diversification of opinion concerning any disease when judged in the light of past experience must mean either that there are many causes of hypertrophic arthritis or that we are dealing with a disease of unknown etiology. Considering the clinical course of the disease and its similarity from patient to patient, the latter possibility seems more likely. Despite this mass of contradictory and confusing information concerning hypertrophic arthritis, most workers agree to two facts, namely, that the disease is present in practically all patients over fifty years of age and that the disease process is primarily one of degeneration of articular cartilage. These two facts are of great importance and must be explained by any theory or study designed to give us a more complete understanding of the origin and nature of hypertrophic arthritis.

Before presenting our experimental and pathological data pertaining to the origin and nature of hypertrophic arthritis, I should like to review briefly certain clinical, roentgenologic and diagnostic facts concerning which most workers agree. Hypertrophic arthritis is chronic in nature and much more frequently encountered than other types of joint disease, including rheumatoid arthritis. Pathological and roentgenological studies reveal that the characteristic changes of hypertrophic arthritis are demonstrable in practically all individuals over fifty years of age despite the fact that many such patients do not admit symptoms. Based on symptomatology alone one encounters a general and a local type. The disease rarely occurs in the monarticular form except in instances where a single joint has been sub-

jected to long continued use or trauma, such as occurs in certain occupational workers. Many patients may complain of symptoms referable to one joint, such as the knee, yet clinical, roentgenological and pathological examinations will reveal hypertrophic arthritis of the same or an even more severe grade in the corresponding joint. In most instances, careful examination will reveal evidence of involvement of articular structures other than those complained of. The joints most commonly involved are the terminal phalangeal joints, the knees, the lumbar spine, the sacro-iliac joints, the lower cervical spine (fourth, fifth, sixth and seventh vertebrae), the shoulders (frequently as a bursitis) and the hips (malum coxae senilis). The midphalangeal joints of the fingers and the metacarpophalangeal joints of the thumbs are less commonly affected. Although no joint is exempt from this disease, these patients rarely complain of symptoms referable to the elbows, wrists and ankles. The involvement is rarely as widespread as in rheumatoid arthritis.

The terminal phalangeal joint lesions are spoken of as Heberden's nodes. Although they are pathognomonic of the disease, they are not present in every patient. They are more common in women than in men. The symptomatology referable to these joints and their appearance varies considerably from patient to patient. In some patients they are never a cause for complaint; some seek medical advice because of their unsightly appearance, others because the joints are sensitive and ache. Some patients desire medical treatment because they fear that such joint signs represent the first objective evidence of a beginning crippling arthritis. In those patients experiencing symptoms with the development of Heberden's nodes, the complaints are aching, tenderness on pressure, slight stiffness, numbness and tingling. Except for the occasional case, there is little to demonstrate at the time of onset other than slight joint swelling. In the exceptional case, early in the disease, the terminal phalangeal joint may be red and bulbous in appearance, fluctuant and tender on pressure. Such signs usually subside in eight to twelve weeks, leaving the tell-tale evidence of the typical Heberden's node. Involvement of all fingers may be present from the onset; more

commonly the joints of the index or the fifth fingers are the first to be affected. All joints may ultimately assume a gnarled, knotted appearance with dislocation of the terminal phalanx to one side because of ligamentous dislocation. Such joints never become truly ankylosed and are usually painless. Rarely a small cyst surmounts the nodosities. Occasionally the midphalangeal joints present the same appearance with or without lateral dislocation of the distal phalanges. In such instances the gnarled appearance of the joint usually distinguishes it from the fusiform appearance so common to rheumatoid arthritis. Furthermore, the hand of the patient with this type of arthritis shows no evidence of atrophy. The grip is strong as compared with the weak, painful, oftentimes flinching handshake of the rheumatoid arthritic.

Patients with hypertrophic arthritis usually have no complaints other than those referable to their joints. When they do, such symptoms are frequently due to disease of some other system. Therefore, the prodromal and constitutional symptoms so frequently observed in rheumatoid arthritis such as weakness, easy fatigability, anorexia, weight loss, fever, tachycardia, vasomotor and neurological-like symptoms are not encountered. The joint symptoms, rarely experienced before the fifth decade, are insidious at the time of onset. An occasional patient with Heberden's nodes will be seen in the thirties and in most such instances there is a family history of the early onset of this affliction. In many patients, particularly in the obese, pain and stiffness in the knees and the back are the first symptoms. In fact the obese patient may develop symptoms at a much earlier period than does the one of normal weight. The symptom of pain in such patients is invariably relieved with bed rest. Some patients may complain of grating and creaking in one or more oi nts with or without associated stiffness, aching or pain. The pain may be accentuated by many factors, particularly by exercise and changes in weather. Generalized stiffness is a common complaint. It is present on awakening or after sitting for a time, only to disappear after walking a short distance or "limbering up." The most distressing symptoms are encountered in

patients with marked deformities of the knees (genu valgum or genu varum deformities) and malum coxae senilis. The latter affliction represents the most disabling and painful manifestation of hypertrophic arthritis. Early the symptoms are mild. When the changes in the head of the femur become marked and the acetabulum deepens, there results marked restriction of motion. Once this stage is reached, pain is a constant symptom, being experienced by so slight an act as turning over in bed. Any or all of the above-mentioned symptoms except those due to advanced malum coxae senilis may fluctuate considerably in certain patients. Some may experience complete freedom for varying periods of time. The reasons for such fluctuations are not always apparent; in some instances, they seem directly related to living in a warm climate. In other patients, although the symptoms are never severe, they continue to persist. In such cases they may be looked upon as a nuisance rather than as a disability.

Patients with hypertrophic arthritis are as a rule well nourished or obese. They do not exhibit evidence of pallor, weight loss, atrophy of skin and muscles, generalized adenopathy, increased vasomotor activity, pigmentation and subcutaneous nodules so frequently observed in rheumatoid arthritis. The examination of the joints is negative, except for restriction of motion demonstrable in malum coxae senilis and marginal proliferation of the terminal phalangeal joints, the knees, the first metatarsophalangeal joints and occasionally the midphalangeal joints. Occasionally one encounters periarticular swelling due to an associated traumatic synovitis. In such cases there may be an effusion.

These patients rarely have anemia; if present, it should be ascribed to some other cause. The same is true of leukocytosis. The sedimentation rate in occasional instances is elevated for some reason as yet unknown. The non-filament count is usually normal. The agglutination tests for streptococci are negative. The uric acid is normal. If elevated, it is probably a reflection of kidney impairment or liver disease. Lowered metabolic rates are encountered no more frequently in this group than in other

individuals of corresponding age. The fasting serum calcium, phosphorus and phosphatase determinations are normal.

A roentgenogram may be negative or show only slight changes; yet when the joint in question is opened, examination may reveal marked changes characteristic of hypertrophic arthritis. Nevertheless, the roentgenographic appearance of hypertrophic arthritis is quite distinct from that of rheumatoid arthritis. Generalized decalcification is not present except as a manifestation of age. The first roentgenographic changes are narrowing of the joint space with sharpening of the articular margins. Subsequently, marginal proliferation and condensation of the subchondral bone ensue. Small cysts are sometimes observed near the articulating surface. Bone destruction and irregularity of the joint line are observed only in well advanced Heberden's nodes. Soft-tissue changes are rarely demonstrable. Ankylosis is seen rarely and then only in the small joints of the spine and in the sacro-iliac joints. One should never let the diagnosis rest solely with the roentgenologist. The roentgenographic findings should be looked upon as one piece of evidence to be considered along with the history, physical examination and other laboratory tests in arriving at a final diagnosis. One must further realize that advanced changes of the hypertrophic arthritic type will often ensue rapidly in a joint previously affected by a gouty, a specific infectious, or a rheumatoid type of arthritis. These should not be confused with primary hypertrophic arthritis.

The diagnosis of hypertrophic arthritis should offer little difficulty in most cases. The history of an insidious onset occurring in the fifth decade of life, persisting for any period of time, practically precludes the existence of most types of arthritis except those which are chronic in nature. The absence of fever, other evidence of infection and obvious periarticular swelling would tend to rule out most of the chronic arthritides due to infectious agents. Although the possibility of chronic fibrositis, metastatic malignancy, arthropathies secondary to disease of the central nervous system and rarely a chronic, specific infectious arthritis would have to be considered, in most instances the diagnosis would rest between that of hypertrophic and rheumatoid

arthritis. The differential diagnosis of these two types of chronic arthritis should be relatively easy if the previously mentioned diagnostic criteria are carefully considered. In an occasional case the passage of time may be necessary before an absolute diagnosis can be established.

In rare cases of hypertrophic arthritis with periarticular swelling and an associated effusion, the clinical differentiation from rheumatoid arthritis may be impossible. In such instances aspiration of the joint and cytological examination of the fluid will furnish the necessary diagnostic help. In hypertrophic arthritis, the average total synovial fluid nucleated-cell count is 500; seldom does it exceed 2,000 per cubic millimeter, and the percentage of polymorphonuclear leukocytes is 10 per cent or less (1). The cytological characteristics of the synovial fluid in rheumatoid arthritis are quite different. Usually the total nucleated-cell count is more than 5,000 per cubic millimeter and the majority of the cells are polymorphonuclear leukocytes. Although the total protein and mucin content and the albumin-globulin ratio are also of diagnostic aid, their determination is rarely necessary (1).

In cases where the symptoms and signs are confined to the terminal phalangeal joints, one must consider other diagnostic possibilities than Heberden's nodes. In rare instances of so-called psoriatic arthritis only terminal phalangeal joint involvement may be present. In such cases the diagnosis rests on the demonstration of psoriatic lesions of the adjacent nail and the finding of psoriatic lesions elsewhere. The nodosities of hypertrophic arthritis should not be confused with the tophaceous deposits of gout which may occur in the region of the terminal phalangeal joints. The latter are more irregularly placed and represent soft-tissue urate deposits which are characteristically yellow or cream colored. The presence or absence of the other manifestations of gout will enable one to establish the correct diagnosis in a questionable case. Occasionally, an acute Heberden's node may be confused with a paronychia. A careful history and examination, however, will prevent this mistake.

As previously stated, all workers agree that hypertrophic

arthritis is primarily a disease of degeneration of articular cartilage, irrespective of cause. The classical description of this type of arthritis most frequently referred to is that of Nichols and Richardson (2). A brief account of what they termed degenerative arthritis will be given for the purpose of orientation.

According to those workers, the first change demonstrable grossly is a loss of the normal translucence and color of the central portion of the articular cartilage. There soon follows a gradual and uneven degeneration of this portion of the articulating surface. This is first evidenced by a fibrillation of the cartilaginous matrix and disappearance of the spindle-celled perichondrium. As a result of this fibrillation the neighboring cartilage cells are set free, finally disintegrating and disappearing. These changes cause the articulating surface to take on a papillary appearance due to the numerous pits, depressions and erosions which ensue. The depth of the fibrillation varies greatly. It may extend through the entire cartilage down to the zone of provisional calcification.* In such instances large masses of articular cartilage may be peeled off, exposing the zone of provisional calcification or the underlying bone to the attrition of joint motion. Although these changes usually involve a large portion of the articulating surface, they are occasionally very localized. In such instances there results thinning or loss of cartilage over a circumscribed area. In order to compensate for the resulting cartilage loss, there occurs an overgrowth of cartilage on the opposing joint surface. This is made possible by an increased activity of the perichondrium. Subsequent to the thinning or disappearance of cartilage, significant changes take place in the underlying or exposed bone. It becomes extremely dense and hard due to thickening of the trabeculae and narrowing of the marrow spaces. The continued friction of joint motion eventually results in complete denudation of the condensed bone. It then assumes an ivory or porcelain-like appearance, a condition called "eburnation of bone." Frequently such eburnated bone displays well-marked parallel or curved grooves.

* We reserve the term "zone of provisional calcification" for the deepest layer of cartilage in growing bone. We prefer the term "calcified cartilage" for that layer of cartilage referred to by Nichols and Richardson as the "zone of provisional calcification."

While this process of fibrillation and degeneration of cartilage is taking place in the central portion of the articular surface, changes of another type are occurring at the peripheral margins. These changes consist of active proliferation of cartilage at the junction of the perichondrium and periosteum. This newly formed marginal cartilage (chondrophyte) may later become transformed into true bone (osteophyte). As a result of this marginal overgrowth there occurs an increase in the size of the bone end. The marginal proliferation is not uniform and in consequence the periphery of the joint becomes irregular in contour. These changes in the shape of the joint surfaces may gradually, over a period of years, lead to subluxation, diminished motion and "ankylosis by deformity."

As a rule, increased thickness of the joint capsule is not observed and in many instances the synovial membrane is normal. When synovial membrane changes are observed, they consist of slight to moderate hyperplasia of the villi accompanied by increased vascularization without histological evidence suggesting infection. Such hypertrophied and pedunculated villi may be converted by metaplasia into cartilage or bone. Loose bodies (joint mice) may result from the detachment of such pedunculated villi or the breaking off of an osteophyte. In this type of joint disease the synovial membrane does not proliferate and extend on to the articular surface as it does in the case of rheumatoid arthritis, and therefore fibrous-tissue ankylosis never occurs. Nichols and Richardson further called attention to the fact that they had never observed any evidence of inflammatory exudation in association with the early degenerative changes of articular cartilage.

If degeneration of the articular cartilage represents the primary change in hypertrophic arthritis, it becomes readily apparent that any study directed at determining the cause of the disease must attempt to explain why such articular-cartilage lesions take place. Consideration of certain anatomical and physiological facts demonstrates that articular cartilage differs in certain respects from other body tissues. It is a relatively avascular tissue, its only direct blood supply being at the periphery from the circulus articuli vasculosus of Hunter. The

central portion is avascular and its exact source of nourishment is unknown. It may be derived solely from synovial fluid, from serum water diffusing through from the subchondral blood vessels or a combination of the two. Reasoning teleologically, one might argue that this restricted source of nourishment is an adequate reason why articular cartilage is a tissue with a low metabolic rate. Knowing these facts one would like to inquire further into the mechanisms responsible for the maintenance and nutrition of normal articular cartilage and its ability to repair itself once injured.

That apposition and weight-bearing are of importance in the maintenance of normal articular cartilage was readily demonstrated in our experiments on dogs in which one leg was amputated at the knee joint (3). In these disarticulated joints, the patellae and patellar ligaments were utilized to cover the femoral articular ends. By careful closure of the synovial membrane and the joint capsule, the end of the femur was enveloped by a sac lined with synovia. When the dogs were sacrificed twelve and twenty-four months later, the synovial-lined sacs were found to contain synovial fluid. The femoral articular ends were quite similar in appearance. The articular cartilage was dull gray in color and showed numerous areas of partial atrophy and degeneration. Gross sections revealed marked atrophy of the subchondral bone. Microscopic examination confirmed this finding. In addition it revealed marked thinning of the cartilage with areas in which complete degeneration had occurred. In some sections, the articular cartilage was covered by fibroblasts which had originated at the perichondrial border. The calcified zone of articular cartilage was reduced in thickness.

Having demonstrated that weight-bearing and apposition are of importance in the maintenance of normal cartilage, we next investigated its ability to regenerate. One might reason a priori that a tissue having a limited source of nourishment and an excess of matrix as compared to cellular elements would repair itself feebly. Information concerning this point was obtained from two types of experimental study: (1) a systematic study of degenerative lesions occurring spontaneously in bovine joints,

and (2) a study of the repair of surgically-created articular-cartilage defects in dogs.

In all cattle over two years of age, there occurs regularly an articular-cartilage defect in the opposing articular surfaces of the carpometacarpal joints (4). Early these lesions appeared as slightly depressed areas. Microscopically one noted thinning of the calcified cartilage layer. The cartilage in the region of the depression showed fibrillation of the matrix with distortion and scattering of the cartilage cells. In the slightly more advanced lesions these changes were more marked and the cartilage definitely thinner. In such instances the calcified zone was markedly thinned, disrupted or absent. The larger defects extended into subchondral bone and were sharply outlined by an irregular margin of overhanging cartilage. Microscopic examination of such lesions revealed that the articular cartilage had completely disappeared and that the defects extended into the subchondral bone. The margins of such defects showed an abrupt transformation from normal hyaline cartilage into fibrocartilage and fibrous tissue. The base of the defects was lined by avascular fibrous tissue which in some instances was replaced by fat tissue. No significant changes were observed in the synovial membrane lining these joints. Most important of all was the fact that we never observed more than minimal evidence of cartilage repair in any of these lesions.

These progressive articular-cartilage defects were considered to be the result of oft-repeated traumatization to the weakly-constructed carpometacarpal articulation in an area where the underlying subchondral bone did not adequately support the articular cartilage. Such trauma to these joints occurs each time a cow lies down or gets onto her feet from the recumbent position.

In order to obtain further information concerning the ability of articular cartilage to regenerate, studies were made of surgically-created defects on the weight-bearing portions of the femoral condyles and in the central portion of the patellar grooves of the knee joints of dogs (3). Such defects were examined four to twenty-eight weeks later. In some of the experiments the defects were extended into the underlying subchondral bone.

From these experiments it was learned that the ability of cartilage to repair itself is very feeble. In some instances no repair occurred. In others repair took place because of proliferation of the cartilage cells. Such repair was most marked in the weight-bearing surfaces of the femoral condyles. In most cases, however, the repairing tissue filled but a small portion of the defect. In those defects located near the perichondrial margins as well as those extending into the subchondral bone the reparative changes passed through stages of fibrous tissue and fibrocartilage to the formation of an imperfect hyaline cartilage. Such fibrous tissue originated in the connective tissue of the marginal synovial membrane, the bone-marrow spaces and in some instances from the articular-cartilage cells. Comparative studies indicate that repair of such surgically-created defects is no more rapid in puppies than it is in adult dogs(5). The presence of such defects was not the cause of intra-articular changes except in those experiments in which the patellae became displaced. In these instances the resulting changes were very similar to those observed in human hypertrophic arthritis.

Knowing that articular cartilage is a tissue with a very limited ability to repair itself, we thought it logical to determine next what changes, if any, occurred in the joints of normal individuals with increasing age (6). For this study we collected a series of knee joints from individuals who, in so far as we could determine, had never had symptoms of joint disease. These joints were obtained at necropsy. At least six knee joints representing each decade of life from the first to the tenth were examined. These joints were studied roentgenographically, macroscopically and microscopically. Such studies revealed that with each succeeding decade of life beyond the second, the knee joint shows increasing pathological changes, degenerative in nature and confined largely to the central portion of the articulating surfaces. There was little or no evidence of attempted repair of these degenerative lesions. Marginal proliferation of cartilage with subsequent transformation into bone was likewise observed. Such changes were demonstrable in all joints from the fifth decade on. The earliest as well as the most advanced changes noted in these

joints were indistinguishable from those commonly spoken of as characteristic of hypertrophic arthritis. Often such changes were not demonstrable by x-ray examination. Arteriosclerosis did not appear to be an important etiological agent. The synovial membrane in such joints was either normal or showed only minimal to moderate changes.

From these studies it is obvious that an individual may have extensive changes characteristic of hypertrophic arthritis, without having symptoms referable to the articular structures. Such observations suggest that these intra-articular changes are the result of increasing age and long-continued use. Because of this suggestion we undertook to determine what changes take place in human joints subjected to unusual use or repeated trauma (7). In such cases, the joint which had been subjected to unusual use or trauma was compared with the opposite joint, which served as the normal control. Instances of this type are readily encountered in various occupational workers. For instance, one woman who had worked as a cutter in a tailoring establishment for fifteen years had a permanent Heberden's node on the thumb of the hand which was used in cutting, but no such nodosities were demonstrable on the other fingers. Roentgenograms of another patient revealed extensive hypertrophic arthritis of the right knee with loose body formation, whereas the left knee showed very minimal changes. On questioning this patient, we learned that she had operated a treadle machine for thirty years. In doing so she was required to flex and extend this knee hundreds of times each day for a period of thirty years. Extensive changes indistinguishable from hypertrophic arthritis were found when the knee was operated upon. Other patients have been observed who demonstrate this same type of intra-articular pathology subsequent to long-continued use. These observations suggest that long-continued use of a joint is an adequate cause for the production of extensive hypertrophic arthritis.

As was previously stated, the knee joints of all dogs in which the patellae became displaced, subsequent to the operative procedure employed, developed extensive intra-articular changes

similar to those of human, hypertrophic arthritis. These observations led to further studies designed to determine the effects of patellar displacement (8). The experiments were performed on rabbits, because in this animal the desired derangement can be produced without opening the joint or otherwise injuring any of the joint structures. Gross and microscopic examination of these joints revealed that anatomical changes similar to those of hypertrophic arthritis occurred as early as four weeks following patellar displacement. The observed changes were much more marked in the experiments of longer duration. Marked lipping of the articular margins of the femur occurred. This was accompanied by degeneration of the original articular-cartilage surfaces and in some instances by eburnation of the denuded bone. Clinical observations demonstrate that extensive intra-articular changes indistinguishable from hypertrophic arthritis occur at a much earlier age in individuals with displaced patellae. These studies suggest that a single joint abnormality (patellar displacement) is of itself an adequate cause for extensive hypertrophic arthritis.

One of the most characteristic roentgenological features of hypertrophic arthritis is the marginal overgrowth or lipping (osteophytes and spurs). Although this marginal proliferation is secondary to the primary degeneration of the central portion of the articular cartilage, its production has never been adequately explained. Certain workers (9) have concluded that such lipping is the result of the marginal bone and cartilage being forced outward as a result of flattening of the joint surfaces. Such an explanation would seem adequate in the case of the extensively altered joints of older people, but it does not explain the lipping observed in younger individuals. In this age-group one notes increasing prominence at the point demarcating the junction of the synovial membrane and the periphery of the articular cartilage before any significant thinning of the cartilage and flattening of the joint surfaces is demonstrable. With increasing age this zone becomes more prominent and in many instances progresses to well-marked lipping.

In the patellar-displacement experiments carried out on rabbits

(7) and in the similar displacements produced accidentally in dogs (3), it was noted that the earliest detectable marginal proliferation occurred at the point where the synovial membrane reflects onto the perichondrium of the articular margins. This marginal zone is very vascular and possesses greater reparative and proliferative ability than do the avascular central areas. That the tissues in this region are subjected to frequent stress and strain can be demonstrated readily by examination of a partially-opened joint. On doing so, one notes that extension and flexion of the joint result in alternating tension and relaxation of the synovial membrane at its insertion. This oft-repeated tension would seem to serve as sufficient stimulus to this vascular fibrous tissue to cause it to proliferate. This proliferating tissue (perichondrial and periosteal), being in intimate contact with cartilage and bone, may become differentiated into fibrocartilage, hyaline cartilage and bone. Once such proliferation has taken place, sufficient alteration in the normal mechanics of the joint ensues to allow these changes to progress more rapidly. Anatomical alterations such as genu valgum, genu varum and patellar displacement undoubtedly increase greatly the stress and strain in this region and, in consequence, there results a more rapid and more extensive marginal proliferation. In one of the rabbit experiments a new articular surface had developed beneath the displaced patella in as short a period of time as four weeks. In another, in which the patellar displacement was of twelve weeks' duration, the articular surface was supported by well-arranged bone trabeculae.

DISCUSSION

From the experimental and pathological data presented, it is obvious that articular cartilage differs from most other body tissues in that it possesses a very limited ability to repair itself. This limitation is not a function of the age of articular cartilage. It would appear much more likely that this restricted reparative ability is directly related to the fact that articular cartilage is a relatively avascular tissue in which the matrix is in great excess to the cellular elements. Certainly it has been adequately

demonstrated that the avascular central portion of the patellar surface of the femur is more limited in its ability to repair itself than are the more vascular perichondrial margins of the femoral condyles. It should, however, be pointed out that the peripheral margins of articular cartilage likewise contain more cellular elements.

These studies further indicate that because of this limited ability of articular cartilage to repair itself, the wear and tear changes of daily life become accumulative with increasing age and in consequence intra-articular changes indistinguishable from hypertrophic arthritis are demonstrable in the knee joints of all individuals over fifty years of age. That the production of this type of joint disease might be explained solely on this basis is suggested by the fact that similar changes ensue if a single joint is subjected to long-continued use or an articular derangement such as patellar displacement. From clinical observations, we further realize that these changes can also be produced or, if present, hastened by increasing the load which a joint has to carry or by impairing its normal mechanics. Such additional factors include obesity, knock knees, bowlegs, fracture into the joint, poor alignment following fractures, severe pronation of the feet, etc. If such factors have been operative since early childhood, hypertrophic arthritis will be demonstrable at a much earlier period than is ordinarily observed. In all probability, the type of cartilage one inherits also governs in part the early onset of hypertrophic arthritis as well as the rapidity with which it progresses.

There may be other factors which injure or impair cartilage and thus allow for the development of this type of joint disease. Any etiological theory concerning the production of hypertrophic arthritis must not lose sight of the fact that all individuals eventually develop it. In other words if there are additional factors which regularly play a rôle in causing this disease, they must affect most human beings.

Degeneration of the mucoid matrix of articular cartilage being the first change observed in hypertrophic arthritis, it is obvious that future studies should be directed toward obtaining more

information concerning its nature, formation and maintenance. For instance, if it could be demonstrated that synovial-membrane permeability decreased with aging, it might then be argued that such degenerative changes are due to poorer nutrition subsequent to a lessened formation of synovial fluid. Similarly if one could prove that a decreased synovial-fluid mucin content was concomitant with increasing age, one might then postulate that poorer lubrication would result, and, in consequence, the wear and tear changes would be more marked. Preliminary studies (10) suggest that a reduced peripheral sensibility with aging may allow for more wear and tear changes without pain than normally occurs. These suggestions and others must be investigated before we can advance our knowledge of hypertrophic arthritis beyond the point we have taken it. Certainly there exists no proof for the various metabolic, endocrine, circulatory, infectious and toxic theories proposed in the past.

The coexistence of hypertrophic and rheumatoid arthritis in the same individual has led some workers to conclude that both diseases are due to the same etiological agent. I cannot subscribe to this unitarian theory. The pathology of these two diseases is in no way similar. It is true that an older individual may develop rheumatoid arthritis with typical fusiform swelling of the midphalangeal joints of fingers exhibiting well-defined Heberden's nodes. In fact, in some individuals, rheumatoid arthritis develops in joints showing advanced hypertrophic arthritis. In the latter instances pathological examination of the joints will reveal evidence of both diseases. Nor should the individual inclined to accept the unitarian theory fail to realize that secondary hypertrophic changes may occur in an old rheumatoid arthritic joint.

If we accept the fact that the primary pathological change in this type of joint disease is one of degeneration and that all other changes are secondary to this primary process, would not the term, *degenerative joint disease*, describe more aptly the pathology of this disease? The word "degenerative" depicts with great exactness the changes which occur in the joints. Therefore, if it were employed regularly to designate this type of disease, it

would automatically portray a picture of the joint pathology. Certainly one might rightly challenge the use of the word "arthritis" when speaking of this type of joint disease, because in this disease, there is little or no evidence of inflammation. For these reasons we prefer the term, *degenerative joint disease*, to designate this type of joint disease.

If we interpret this disease as being primarily degenerative in nature, what bearing does this have on the symptomatology, prognosis and treatment? If the marginal-tissue proliferation takes place rapidly, there will follow rapid elevation of the periosteum with pain. Once the proliferation of the marginal osteoid tissue ceases and it becomes calcified, pain may no longer be present. If such proliferation is gradual, then little or no pain may be experienced. Heberden's nodes behave in this same manner, being painful when acute and painless when quiescent. In some instances they produce little or no pain. Such natural variations in the course of the disease illustrate how difficult it is to interpret the results of therapy directed at the control of this type of pain. The other causes of pain are altered mechanics and, occasionally, impingement of a pedunculated villus, or loose body formation. In the latter instances, surgery offers the only hope of alleviation of pain.

The patient is most concerned with the prognosis pertaining to his disease. Patients with this disease (with the exception of malum coxae senilis) can be assured that they are not suffering from the chronic, progressive type of arthritis and therefore will not become crippled. Joint deformities, subluxations and restriction of motion may result, but true ankylosis almost never occurs.

It is fair to assume that once the degenerative changes have taken place they cannot be cured, because of the limited ability of articular cartilage to repair itself. If, however, any causative or contributing factors can be corrected or removed, it seems reasonable to assume that the process may be arrested or its rate of progress retarded. These patients should not be subjected to the various therapeutic procedures advocated by the adherents of the metabolic, endocrine, circulatory, infectious and toxic theo-

ries. True, a low caloric diet will often result in sufficient weight reduction to bring about painless knees. In such instances, however, the weight reduction is the all-important factor, and not any one special dietary feature. Weight-reduction, if indicated, rest, physical therapy, correction of faulty mechanics and reassurance are the most important factors in the treatment of this disease. The disabling symptoms of malum coxae senilis are usually improved following a Smith-Petersen acetabuloplasty (11). These patients must be reassured that they are not headed for crippledom and a life of invalidism.

CONCLUSIONS

1. Hypertrophic arthritis is due primarily to the wear and tear subsequent to the daily use of articular cartilage, *a tissue possessing a limited ability to repair itself*. The process may be accelerated by unusual use and repeated trauma.

2. The primary change in hypertrophic arthritis is degeneration of the mucoid matrix of articular cartilage; therefore, future studies concerning the further elucidation of this type of joint disease must attempt to determine the nature, formation and maintenance of this mucoid matrix.

3. We prefer the term, *degenerative joint disease*, because it describes more accurately the pathological changes encountered.

REFERENCES

(1) Unpublished data.

(2) Nichols, E. H., and Richardson, F. L.: Arthritis Deformans. *J. Med. Research*, 1909, **21**, 149.

(3) Bennett, G. A., Bauer, Walter, and Maddock, S. J.: A Study of the Repair of Articular Cartilage and the Reaction of Normal Joints of Adult Dogs to Surgically Created Defects of Articular Cartilage, "Joint Mice," and Patellar Displacement. *Am. J. Pathol.*, 1932, **8**, 499.

(4) Bennett, G. A., and Bauer, Walter: A Systematic Study of the Degeneration of Articular Cartilage in Bovine Joints. *Am. J. Pathol.*, 1931, **7**, 399.

(5) Bennett, G. A., and Bauer, Walter: Further Studies Concerning the Repair of Articular Cartilage in Dog Joints. *J. Bone and Joint Surg.*, 1935, **17**, 141.

(6) Bennett, G. A., and Bauer, Walter: Degenerative Changes in Joints Resulting from Continued Trauma and Increasing Age, and Their Relation to Hypertrophic Arthritis. *Am. J. Pathol.*, 1933, **9**, 951. Also, unpublished data.

(7) Bauer, Walter, and Bennett, G. A.: Experimental and Pathological Studies in the Degenerative Type of Arthritis. *J. Bone and Joint Surg.*, 1936, **18**, 1.

(8) Bennett, G. A., and Bauer, Walter: Joint Changes Resulting from Patellar Displacement and Their Relation to Degenerative Joint Disease. *J. Bone and Joint Surg.*, 1937, **19**, 667.

(9) Parker, F., Jr., Keefer, C. S., Myers, W. K., and Irwin, R. L.: Histologic Changes in the Knee Joint with Advancing Age. Relation to Degenerative Arthritis. *Arch. Pathol.*, 1934, **17**, 516.

(10) Corbin, K. B. Alterations in the Hip Joint After Deafferentation. *Arch. Surg.*, 1937, **35**, 1145.

(11) Smith-Petersen, M. N.: Treatment of Malum Coxae Senilis, Old Slipped Upper Femoral Epiphysis, Intrapelvic Protrusion of the Acetabulum, and Coxae Plana by Means of Acetabuloplasty. *J. Bone and Joint Surg.*, 1936, **18**, 869.

Diabetes Mellitus in the Light of Our Present Knowledge of Metabolism*

By C. N. H. Long, M.D.

Sterling Professor of Physiological Chemistry, Yale University School of Medicine

INTRODUCTION

At the present time diabetes mellitus may be defined as a disorder either of the chemical changes undergone by protein, fat, and carbohydrate in the living organism or of the regulatory mechanism by which these changes are adjusted in relation to each other.

When we speak of a "normal" metabolism we imply that both these chemical changes and the regulatory mechanisms governing them are so adjusted in their relation to each other that the constituents of the tissues and body fluids are held within comparatively small limits under a wide variety of dietary and other circumstances.

Now, as we have come to realize that a variety of factors determine the normal metabolism, so we must also consider that the clinical condition known as diabetes mellitus may be brought about by the perverted activity of several agents whose normal functions are directed towards different ends. It is only by recognizing this that we can hope to understand the occurrence of the cardinal symptoms of diabetes, hyperglycaemia and glycosuria in such apparently different conditions as destruction of the pancreas, tumours of the pituitary, adrenal cortex, ovary or thyroid, as well as in those cases in which no demonstrable lesion can be found at autopsy.

The frequent presence of glycosuria in conditions other than those associated with disease of the pancreas has been known for a considerable length of time. The importance of this fact in

* Nathan Lewis Hatfield Lecture XXII, College of Physicians of Philadelphia, February 1, 1939.

our understanding of the etiology of the majority of cases of diabetes has been considerably lessened by three factors: (a) the lack of experimental evidence implicating any organ other than the pancreas in the control of metabolism and (b) the easily discernible fact that the great majority of diabetics did not carry any obvious stigmata known to be associated with pituitary or adrenal dysfunction. (c) The results of total pancreatectomy in certain species of animals presents such a close parallelism with those seen in clinical diabetes that it is not surprising that the view has gained general acceptance that all cases of diabetes are to be attributed to a greater or less degree of insulin deficiency.

It is far from my intention to contend that insulin deficiency is still not of paramount importance in our understanding of this disease, but I would like it equally well understood that neither the occurrence of pancreatic lesions in a large number of diabetics, nor the success of insulin in abolishing glycosuria in an even greater number, is conclusive proof of the universal occurrence of insulin deficiency. Indeed, as many have pointed out before me, at least 25 per cent of autopsies on diabetics reveal no pancreatic lesion nor does assay of the pancreas always disclose an inferior content of insulin. Since insulin will also abolish glycosuria due to a wide variety of agents, its effect in diabetes is not a specific one; and in consequence caution should be used in interpreting its action in this condition as any such proof.

It is my purpose this evening to bring before you certain new facts concerning the control of metabolism that even at the present time have brought about a reorientation in our understanding of the manner in which a normal metabolism is maintained, and since we are agreed that diabetes mellitus is accompanied by marked perversions of metabolism, it does not seem imprudent even at this early date to re-examine our present views as to its etiological basis in the light of this new knowledge.*

* However, diabetes is not the only disorder of metabolism seen in the clinic, and equal stress might be laid on the relation of this newer knowledge to such conditions as chronic hypoglycaemia, thyroid disease, Addison's disease, or in fact to any condition in which alterations of the normal processes of metabolism occur.

SOME GENERAL CONSIDERATIONS OF THE METABOLIC ACTIVITY OF THE ENDOCRINE GLANDS

The simplest types of organisms, such as yeasts, do not possess special groups of cells that secrete chemical substances capable of altering the metabolism of the whole organism. Nevertheless, they possess the ability to bring about major transformations of their food materials in a manner and at a rate that compares favorably with, and often exceeds, that found in the higher organisms possessing an intricate system of endocrine glands. Thus Wierzuchowski (1) has shown that the oxidative consumption of glucose by yeast on a weight basis is some thirty-six times that of the dog.

In the higher organism, however, the regulation of metabolism is strikingly dependent on the endocrine glands and not only dependent on their presence as single individuals, but also on the proper interaction amongst them as a group. Consequently, the absence or deficiency of any particular secretion not only deprives the organism of a substance probably required to catalyse a particular chemical change, but in addition may induce the following sequelae:

(a) An accumulation of metabolites in quantities not normally found, which accumulation may still further weaken the defective endocrine gland by stimulating it to further secretion. Such a vicious circle is seen with its full consequences in a partially depancreatized animal fed large quantities of carbohydrate. (b) A relative or absolute increase in the activity of other endocrines which normally affect metabolism in an opposite manner to the defective member. In consequence, conditions associated with an apparent hyperactivity of certain endocrine glands are frequently superimposed on an endocrine hypofunction. Such a result is seen in the relative hyperactivity of the anterior pituitary following pancreatectomy, thyroidectomy, or castration. (c) In the special case of the anterior pituitary, an alteration in its secretory activity brings about both widespread functional and anatomical changes in several other endocrine glands; and in consequence it is in diseases involving this organ that the term "polyglandular syndrome" finds its proper application.

Conversely, when one member of the endocrine system be-

comes hyperactive certain other sequelae are likely to follow:

(a) An acceleration of certain phases of metabolism which lead to the accumulation of intermediary metabolites at a rate beyond the immediate capabilities of the organism to dispose of.

(b) A subsequent compensatory activity of other endocrines: e.g., the enlargement of the adrenal cortex in hyperthyroidism.

(c) When the anterior pituitary is the organ involved, a simultaneous hyperactivity of several endocrine glands.

Finally, under the special circumstances induced by the injection of an excess of hormone into a normal animal alterations in the other endocrine glands of a still different character may occur. Thus, an excess of the cortical hormone leads to *atrophy* of the cortex of the adrenal (Ingle, Higgins and Kendall, (2)), and it is reported that the continued injection of insulin into normal individuals is followed by a decreased secretory activity of the islands of Langerhans. Furthermore, such an excess of hormone frequently affects other endocrine glands besides that from which it is derived, as, for example, the atrophy of the adrenal cortex following the injection of the female sex hormones.

It should also always be remembered that the various metabolic hormones may affect different organs in a different manner, or their action may be limited to a single organ.

THE RELATION OF GLYCOSURIA TO HYPO- AND HYPERACTIVITY OF THE ENDOCRINE GLANDS

The generalizations outlined above emphasize the complexity of the problem that is presented by the occurrence of glycosuria. Glucose is a substance that can be produced and utilized in large quantities by the organism, and in consequence a quantity exceeding the immediate resources of the body to dispose of may accumulate (a) by a defect in the mechanism for its removal, or (b) by an acceleration of the metabolic processes concerned with its production. These possibilities may be further subdivided into defects or excesses due to hypo- or hyperactivity of the endocrine glands concerned or to aberrations in the activity of the organs chiefly concerned with its metabolism.

(a) *Pancreatic insufficiency.* Glycosuria resulting from a defi-

cient endocrine function is exemplified by its occurrence following either partial or total removal of the pancreas and until recently this was the only procedure by which glycosuria at all resembling that seen in human diabetes could be produced. The characteristic features of this condition are not only the presence of glucose in the urine, but the concomitant disturbances in fat and protein metabolism as indicated by the occurrence of acetonuria and an increased nitrogen excretion.

The interpretation of the manner in which pancreatectomy causes profuse glycosuria associated with an increased metabolism of fat and protein has been the subject of some difference of opinion. One group, in part basing their conclusion on the absence of any evidence to indicate hyperactivity of any endocrine gland following pancreatectomy, has stated that the whole picture of total pancreatic diabetes is a consequence of the absence of insulin; while another has presented the view that the uncontrolled activity of other endocrine organs plays an equal, if not a major, rôle.

(b) *Temporary or permanent glycosuria following injections of anterior pituitary extracts.* The discovery by Houssay (3) that the injection of anterior lobe extracts into normal dogs resulted in a severe, temporary, glycosuria, so long as the injections were continued, has received wide-spread confirmation and at once offers the first concrete evidence that an extra pancreatic factor could precipitate a glycosuria comparable to that produced by insulin deficiency. This has been followed by the even more striking experiments of Young (4) that have already been confirmed by Campbell and Best (5) and by Dohan and Lukens (6).

Young found that if dogs (and these animals seem to be particularly susceptible) were injected daily for two to three weeks with massive doses of crude anterior pituitary extract not only was glycosuria produced, but this continued for as long as a year after the cessation of the injections. Furthermore, like the glycosuria following pancreatectomy, it continued during fasting and was accompanied by acetonuria. There are, however, certain differences between the behavior of these animals and those subjected to total pancreatectomy. In addition to the

long survival there does not appear to be the intense stimulation of protein and fat metabolism that is seen in totally depancreatized dogs.

Although a final answer cannot be given at the present time as to the exact manner in which the anterior pituitary influences metabolism, enough is known to indicate that this effect does not require the presence of the pancreas. Indeed, these extracts exhibit their most intense action in animals with the mild diabetes that follows the removal of both pituitary and pancreas. Furthermore, a partially depancreatized animal is much more susceptible than a normal one.

Nevertheless, a further study of the permanent diabetes produced in dogs by anterior pituitary extract has indicated that the pancreas is not normal. This is shown not only by the degeneration of the islet cells that occurs, but also by the reduction in their insulin content, (Richardson and Young (7), Campbell and Best (5), Dohan and Lukens (6), Houssay and Foglia (8)). Thus, although the effect of this extract is not a direct one upon the pancreas, nevertheless its continued operation results in an insulin deficiency no doubt due to the strain imposed upon this organ by the high blood glucose level that is present.

The importance of Young's experiments lies not only in the beautiful demonstration of the insufficiency of one member of the endocrine system produced by an excess of another hormone; these experiments have a very pertinent place when we consider the etiological factors precipitating human diabetes. It will be observed that, although the period of hyperpituitarism induced by the anterior pituitary extract injections only lasted two or three weeks, yet their effects were perpetuated for months by the permanent alterations in the endocrine system that they produced. I have previously pointed out that at the time of the discovery of their disease only a relatively small number of diabetics present frank signs of hyperpituitarism. Could not, however, such a phase of hyperpituitarism long since have passed, leaving none of the characteristics of a long-continued excess of these hormones but only the evidence of its temporary

occurrence in the permanent alterations produced in their metabolism?

Apart from hyperactivity of the pituitary due to pathological causes it is well known that one period of life, at least in women—the menopause, is characterized by marked physiological hyperactivity of this gland. This occurs between the fifth and sixth decade at which period the onset of diabetes far exceeds that in any other similar period.

THE METABOLIC HORMONES OF THE ANTERIOR PITUITARY

The work of Houssay and Young raises as many questions as it answers, if not more. This is partly on account of the particular relationship of the anterior pituitary to the other glands of internal secretion, and partly by reason of the large number of substances that are claimed to be secreted by this gland and which are stated to have specific effects on metabolism. The question as to the mediation of the effects of the anterior pituitary on metabolism by other endocrine glands we may leave for a moment and consider the various claims that have been put forward as to the nature of the metabolic hormone or hormones.

Table 1 lists nine anterior pituitary hormones that have been described as influencing metabolism in one manner or another. Now, it is obviously unlikely that the anterior pituitary actually does secrete this number of metabolic hormones, and it is certain that further chemical fractionation will reduce this number. However, passing over this consideration the table lists four main effects attributed to these various extracts: (a) the production of hyperglycaemia and glycosuria by inhibition of carbohydrate utilization, as is indicated by the depression of the R. Q. in fed animals. With this may probably be coupled the effect of these extracts in preventing the depletion of muscle glycogen in hypophysectomized animals and increasing it in the fed normal animal (glycostatic action of Russell (9)). (b) The production of fatty infiltration of the liver, lipaemia and acetonuria. (c) Inhibition of the action of *exogenous* insulin (glycotropic action of Young (10)). (d) The reduction of blood N.P.N. and urine nitrogen

TABLE 1

Hormones affecting metabolism ascribed to the anterior pituitary

	Effect produced	Suggested mode of action	Name of hormone	Heat stability	Ultra-filterable
1	Hyperglycaemia, glycosuria; depression of R.Q.; permanent diabetes	(a) Inhibition of carbohydrate utilization; (b) stimulation of gluconeogenesis	Diabetogenic (Houssay)	Labile	No
2	Prevents depletion of muscle glycogen in fasted hypophysectomized animals	Inhibition of carbohydrate utilization in the muscles	Glycostatic (Russell)	Labile	No
3	Hyperglycaemia and increased liver glycogen	Stimulation of adrenal cortex, gluconeogenesis from protein	Adrenotropic (Bennett)	Stable	No(?)
4	Ketosis, hyperglycaemia; inhibits insulin action; depresses R.Q.	(?)	Intermedin(?) (Collip)	Stable	Yes
5	Inhibits action of insulin	(?)	Glycotropic (Young)	Stable	No
6	Ketosis, lipaemia; fatty livers	Stimulation of fat metabolism	Ketogenic fat metabolism hormone (Anselmino, Magistris)	Labile	Yes
7	Increases liver glycogen	(?)	Carbohydrate metabolism hormone (Anselmino)	Labile	Yes
8	Decreases blood sugar and liver glycogen	Stimulation of the Islands of Langerhans	Pancreatotropic (Anselmino)	Labile	Yes
9	Decreased blood N. P. N. and urine nitrogen; decreased blood sugar; depresses R.Q.	(a) Protein synthesis or (b) inhibition of protein catabolism	Growth (Evans, Teel, Harrison, Gaebler)	Labile	No

(growth promoting effect), (Teel and Watkins (11), Gaebler (12), Lee (13)). The existence of the so-called pancreatotropic factor of Anselmino and Hoffman, which is said to induce a secretion of insulin and a fall in blood sugar, has not been confirmed by Richardson and Young (14).

It is my belief that it is dangerous at the present time to advance the view that the metabolism of carbohydrate, protein and fat is controlled in a separate manner by specific anterior pituitary hormones. This is particularly so in the case of the fat metabolism, as the following considerations will indicate. (a) A suppression of carbohydrate utilization must increase the proportion of fat undergoing catabolism—a situation in which movement of the depot fat to the liver and acetonuria is known to occur. (b) The remarkable fact that the so-called "growth promoting" fraction of the anterior pituitary can remove a considerable portion of protein from catabolism both in fed and fasting animals implies that an isocaloric equivalent of carbohydrate or fat must be substituted for the protein thus withdrawn.

These considerations merely emphasize the established view that the organism can vary the composition of metabolic mixture over a wide range, making use of those foodstuffs that are most immediately available for its needs.

A further word may be said about the growth promoting factor. There is now no doubt of the spectacular effect of fairly purified extracts of the anterior pituitary in re-establishing growth in hypophysectomized animals or increasing the rate of growth in normal animals. Now, it is idle to assume that such a complex phenomenon as growth is determined solely by an anterior pituitary hormone. Such an assumption relegates to a minor and inexplicable rôle the effects on growth of vitamins, other hormones and essential amino acids. The real part played by the growth promoting hormone would appear to be its ability to divert the protein metabolism of the cell towards the synthetic phase or at least to temporarily increase the storage of protein, probably in the liver (Lee (13)).

Such an increased rate of protein synthesis must in some manner be a necessary prerequisite for cellular divison and

growth. In the higher organisms, beyond a certain age, this pituitary factor appears essential for such a synthesis.

In support of the contention that the essential relationship of the anterior pituitary to growth is its effect on the protein metabolism of the cells, it may be pointed out that Harrison and I have found that urinary nitrogen retention may be brought about by suitable anterior pituitary extracts in *fasting* rats (Table 2). Here, of course, the term "growth promoting" becomes an obvious misnomer and such an effect only becomes reasonable if we assume that even during fasting this hormone enables the cells to reduce the rate of protein catabolism.

The relationship between the anterior pituitary and certain aspects of growth has more than a passing interest to students

TABLE 2

Effect of saline extract of anterior pituitary on normal fasting rats (Harrison)

	Urine		Blood	
	Nitrogen	Acetone bodies	Glucose	N. P. N.
	mgm./24 hours	*mgm./24 hours*	*mgm. per cent*	*mgm. per cent*
Untreated (10)	89 ±3.3	1.0 ±0.6	85 ±3.9	49 ±2.9
A.P.E. (12)	64 ±3.1	13.2 ±3.5	55 ±3.2	33 ±1.9

All rats fasted 72 hours. A.P.E. given twice during last 48 hours.

of juvenile diabetes, for Priscilla White (15) and others have found that prior to the onset of this disease many children are overheight for their age. This may well be an indication of an excessive activity of the anterior pituitary which, under the right circumstances, may ultimately precipitate the characteristic metabolic disturbances of diabetes mellitus.

I am also inclined towards the view that the rapid development of fasting ketosis in children is related to the presence in the body fluids at this age of higher levels of growth promoting substance than are to be found in later life. Since, as we have seen, the protein sparing action of this hormone is exerted even during fasting it does not seem irrational to suppose that this may be a more important factor in precipitating ketosis than the supposed rapid depletion of liver glycogen.

We may conclude this survey of the metabolic activities of anterior pituitary extracts by pointing out that the chemical separation of the hormones has not yet proceeded to the point where we can assign one or more of these activities to a definite principle. On the other hand, there is no doubt that this gland exerts a major influence on metabolism. Animals deprived of their anterior pituitary oxidize an abnormal proportion of fed carbohydrate, are extremely sensitive to insulin, and when fasted rapidly deplete their glycogen stores both in liver and muscles and frequently succumb to the profound hypoglycaemia that develops (Russell and Bennett (20a)). All of these changes may be prevented by anterior pituitary extracts; and these extracts in normal animals bring about alterations that result in a decreased level of carbohydrate utilization and a transfer of the bulk of metabolism to that of fat (Russell (20b)), Lee (13)).

It is evident that the preservation of a normal metabolism is determined by the equilibrium established as a result of the activity of those hormones that inhibit or accelerate either directly or indirectly the utilization and storage of protein fat or carbohydrate. In the absence of the anterior pituitary the organism cannot establish an equilibrium between carbohydrate utilization and production (or supply) nor between protein catabolism and anabolism. On the other hand, an excess of anterior pituitary reduces carbohydrate utilization to a point at which the metabolism of fat predominates to an unusual degree.

THE RÔLE OF THE OTHER ENDOCRINE GLANDS IN THE CONTROL OF METABOLISM

I have spoken thus far of the anterior pituitary hormones as though they exerted a direct effect upon the metabolism of the tissues and have ignored the important fact that the function of certain other endocrine glands of metabolic significance is controlled to a major degree by the level of activity of the anterior pituitary.

The question as to whether the alterations in metabolism produced by hypophysectomy or by A.P.E. are dependent either in whole or in part on the presence of one or more of these other

endocrine organs is one that has given rise to some difference of opinion. This, like so many similar differences, appears to be resolving itself into a situation that is satisfactory to both points of view.

Following the demonstration, in 1929, by Houssay (3) that hypophysectomy attenuated the rapidly severe diabetes following total pancreatectomy in the dog, Lukens and I pointed out (16) that an almost identical change in the metabolism of total pancreatic diabetes could be brought about in the dog and cat by removal of all adrenal cortical tissue. At that time we were unable to aggravate this mild diabetes by the injection of anterior pituitary extract or by what we considered to be large quantities of adrenal cortical extract. In view of this we suggested that part of the effect of hypophysectomy was due to the adrenal cortical atrophy that follows this operation, but we were unable to put forward any satisfactory suggestion as to why cortical extract was also inactive.

This earlier failure of Lukens and myself to intensify the diabetes of adrenalectomized depancreatized animals with cortical extract was, I am now sure, entirely due to inadequate dosage, and in more recent experiments Lukens and Dohan (24) have reported the aggravation of diabetes in these animals by the use of large doses. In New Haven my colleagues and I have had similar results, using a different test animal. This is the partially depancreatized rat, first described by Shapiro and Pincus (17). Since these animals are likely to have an extensive usefulness in the study of metabolism a few words about their preparation and characteristics may be given.

Young male rats of 21–25 days of age and weighing, in our colony, from 60–70 gms. are partially depancreatized by excision of the splenic portion of the pancreas and as much more tissue as can be removed without injury to the mesenteric blood vessels and the common bile duct. The animals are then allowed to reach a weight of 200–300 gms., at which time some 30 per cent will be found to have permanent glycosuria. With rigid control of the diet and careful urine collection the level of glycosuria under a given regime is very constant and, what is more important, it

persists at a given level for long periods (*Table 3*). The severity of the diabetes varies somewhat in different animals, but may be of such an extent that 60 per cent of the available glucose of the diet is excreted. In spite of this the animals remain healthy, some of them gaining weight while others undergo a gradual loss. The quantities of glucose excreted reach high levels and on a comparative basis far exceed those found in human diabetes and in total diabetes in dogs. Thus, it is not unusual for a rat of 300 grams to excrete 8–10 grams of glucose daily, although such rats, in our experience, do not develop any appreciable degree of

TABLE III

Daily variation of glycosuria in partially depancreatised rats

Rat number	Age*	Body weight*	Period	Urine volume	Urine glucose		Per cent of available glucose excreted	Changes in body weigbt	Diet
					Grams/day	Coefficient of variability			
	days	*grams*	*days*	*cc./day*				*grams/day*	*grams/day*
76	162	271	63	92	4.3 ±0.1	15.8	37.2	+0.1	45
78	401	280	31	94	5.1 ±0.3	27.4	31.4	+1.9	50
79	170	324	50	83	4.4 ±0.1	14.7	37.9	−0.9	45
81	224	329	49	86	4.4 ±0.1	15.6	40.7	−0.8	42
85	230	321	40	77	2.2 ±0.1	30.0	17.0	+1.7	50
102	61	220	39	68	4.0 ±0.1	13.6	36.3	+1.6	35
100	73	230	21	99	6.6 ±0.3	17.7	50.7	+0.6	40
103	82	225	30	82	5.4 ±0.2	22.4	41.5	+1.4	40
111	96	182	25	99	6.9 ±0.1	8.1	50.7	+0.2	42

* Age and body weight at beginning of period.

ketosis. In fact we have never observed it unless they are intensively treated with anterior pituitary extract. One rat in our laboratory has been diabetic for upwards of two years—a long time for even a normal rat to survive.

The rats that do not exhibit permanent glycosuria under these conditions are ideal preparations for the demonstration of the glycosuric action of hormones. *Figure 1* shows the development of permanent glycosuria following injection of anterior pituitary extract in one of these originally aglycosuric rats, an experiment comparable to that of Young's on normal dogs.

These frank or potentially diabetic rats offer many advantages as experimental animals: (a) use of large numbers at low cost of maintenance, (b) ease of adrenalectomy, hypophysectomy, etc.,

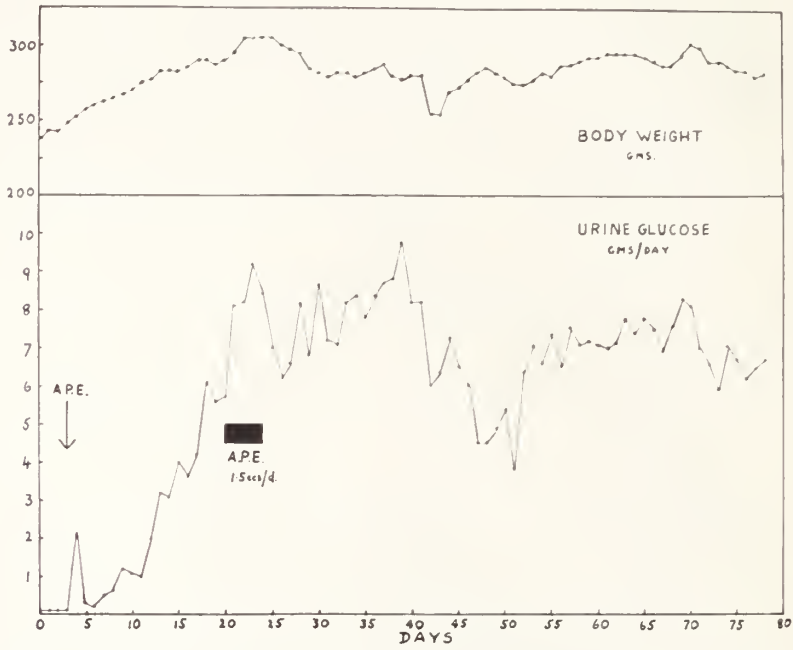


Fig. 1. The effect of a saline extract of the anterior pituitary on inducing a permanent glycosuria in a partially depancreatized rat.

(c) inbred strains with remarkably constant metabolic characteristics.

The effects of adrenalectomy and cortical hormones on the diabetes of partially depancreatized rats

By the use of these partially depancreatized rats we have been able not only to confirm the original experiments on the effect of adrenalectomy in attenuating a pancreatic diabetes, but also the following important points with regard to the rôle of the adrenal cortex in metabolism: (a) the grafting of young rat cortical tissue into adrenalectomized depancreatized rats restores, after a latent period, the glycosuria; (b) the administration of either cortical

extract or the crystalline compounds A and B, isolated from the adrenal cortex by Kendall, causes a recrudescence of the glycosuria of adrenalectomized depancreatized rats (*Figure II*). The amount of cortical extract required when given by mouth to restore the glycosuria to its original level is from 2–3 cc. per 100 gms. rat. The large quantity required explains the earlier failure

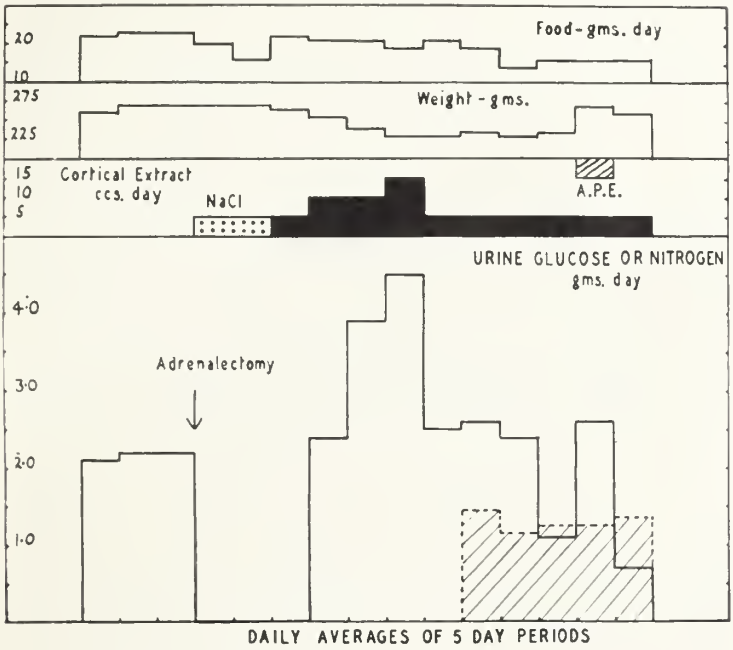


Fig. II. The effect of adrenalectomy and subsequent oral treatment with cortical extract (Upjohn) on the glycosuria of a partially depancreatized rat. It will be observed that anterior pituitary extract (A. P. E.) still further increases the glycosuria when the animal is receiving a constant quantity of cortical extract.

of Lukens and myself to influence the glycosuria of our adrenalectomized depancreatized cats, since in these experiments the amounts given were too small, even if it be assumed that the requirement of the cat is much less than that of the rat. This finding also shows that the adrenal cortical factor maintaining life and influencing the water and electrolyte metabolism is identical with that controlling the carbohydrate metabolism; (c) finally,

the daily ingestion of cortical extract or the crystalline compound B (corticosterone), isolated from the adrenal by Kendall, will induce glycosuria in an aglycosuric depancreatized rat or exaggerate that of an animal with permanent glycosuria (*Figure III*). This effect is strikingly akin to that produced by A.P.E. and has a direct bearing on the question of the participation of the adrenal cortex in the effects of the metabolic activities of the anterior pituitary.

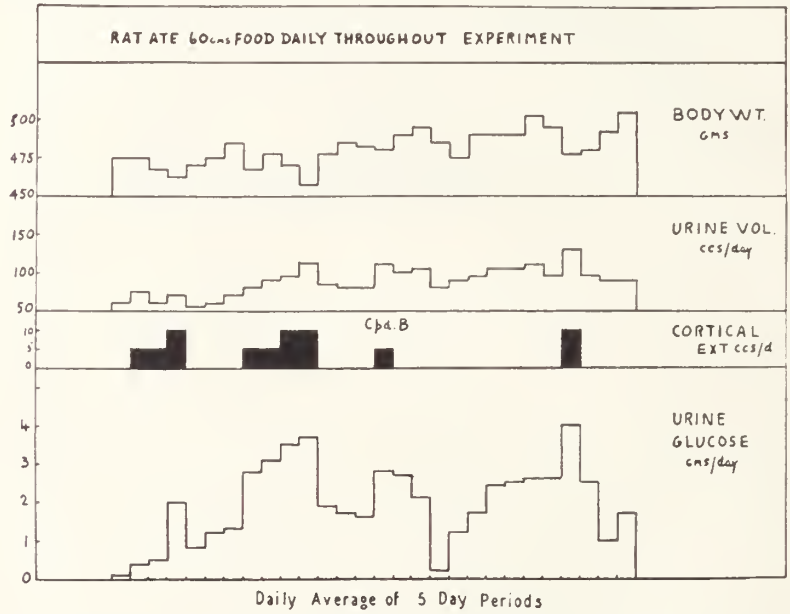


Fig. III. The induction of glycosuria in a partially depancreatized rat following the oral ingestion of cortical extract or the crystalline cortical compound B of Kendall.

The restoration of the glycosuria of adrenalectomized depancreatized rats by cortical extract does not definitely prove that the adrenal cortex is directly responsible for this effect. This is on account of the fact that adrenal insufficiency, particularly in the late stages, is characterized by profound alterations in the whole economy of the organism, to which general cause rather than to the loss of a specific hormone the declines in blood glucose and liver glycogen might be attributed. Indeed, several investi-

gators have inclined to the view that any beneficial effect of cortical extracts on the carbohydrate metabolism of adrenalectomized animals is due to the improvement in their general condition and is not a direct effect of the hormone administered.

This argument has a certain amount of justification so long as it can be shown that the effect of adrenal cortical extract on carbohydrate metabolism is limited to animals in the shocked condition that is characteristic of the last stages of adrenal insufficiency. However, if it can be shown that *supernormal* levels of liver glycogen and blood glucose are produced by high levels of dosage in adrenalectomized animals this argument loses much of its force.

As a matter of fact, the early work of Britton and Silvette (18) showed that adrenal cortical extracts did elevate the carbohydrate stores of adrenalectomized animals well beyond normal limits, a result that Katzin and I have confirmed (19). Furthermore, in the adrenalectomized depancreatized rat shown in *Figure II*, the administration of cortical extract elevated the glycosuria to more than twice the level existing *before* adrenalectomy.

THE EFFECT OF ADRENAL CORTICAL HORMONES ON THE CARBOHYDRATE METABOLISM OF NORMAL ANIMALS

Of even greater importance is the demonstration that adrenal cortical extract or crystalline cortical hormones will elevate the blood glucose and liver glycogen of both fed and fasted *normal* animals. The earlier experiments of Britton and Silvette (18) indicated this, and the more recent work of Katzin and myself has confirmed and extended their work (*Figure IV*).

The remarkable increases in liver glycogen even in fasted animals explains why these extracts aggravate the diabetes of partially depancreatized rats. We have not succeeded in producing glycosuria in normal rats, but since we have also failed to do so with massive doses of anterior pituitary extract, it perhaps may be concluded that this species is more resistant than the dog to "diabetogenic" hormones.

The effect of cortical hormones in increasing the carbohydrate levels of both adrenalectomized and normal rats furnishes a

reasonable explanation for the occurrence of glycosuria in individuals with tumours or hyperplasia of the adrenal cortex and implicates both the anterior pituitary and adrenal cortex in the control of carbohydrate metabolism since, as we have seen, the functional

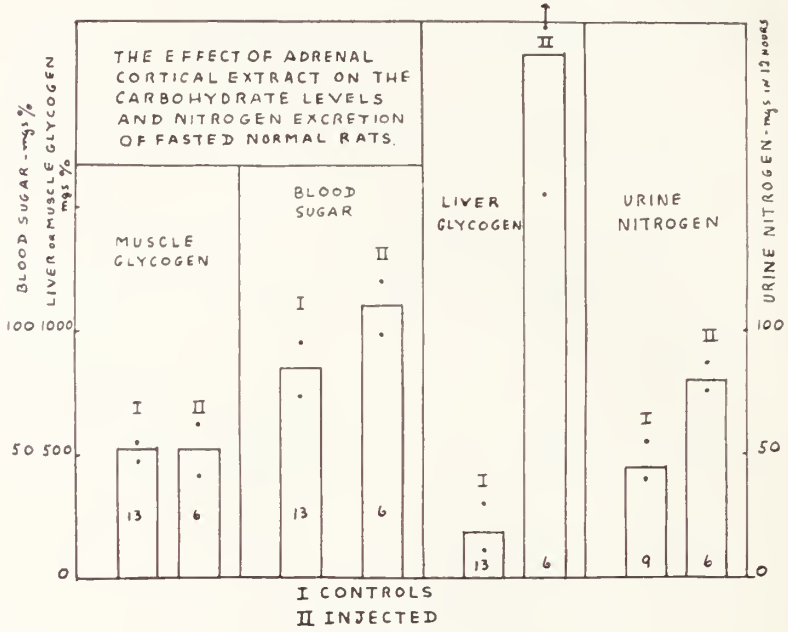


Fig. IV

integrity of the latter is largely dependent on the secretion of adrenotropic hormone by the former.

The Mechanism of Action of Adrenal Cortical Hormones on Metabolism and the Adrenal Cortex-Anterior Pituitary Relationship

I have already indicated the experiments that lead to the conclusion that the effect of the adrenal cortical hormone on carbohydrate metabolism is a positive one and is not limited to animals in adrenal insufficiency. The main features of this effect are a marked increase in the blood glucose and liver glycogen of

both fed and fasted animals with a smaller increase in the muscle glycogen.

Now, the fact that in a fasting animal the carbohydrate stores are increased several times above the normal level can only mean that under the influence of this hormone a new formation of carbohydrate has occurred. Since the usually accepted source of such carbohydrate is protein, Katzin and I (unpublished experiments) have made a careful study of the nitrogen excretion of normal fasted rats when injected every hour for 12 hours with 1 cc. of Upjohn's cortical extract. In almost every case there is a 30–40 per cent increase in nitrogen excretion, indicating an increased protein catabolism in a quantity sufficient to account for the newly formed carbohydrate in the tissues and body fluids (*Figure IV*).

We must now consider the situation that has evolved. In the first place, the injection of crude anterior pituitary extracts into partially depancreatized or normal animals leads to hyperglycaemia and glycosuria, while in normal animals it always results in a suppression of carbohydrate utilization, and in some species to glycosuria as well. On the other hand, the injection of cortical hormone into partially depancreatized rats results either in the appearance or exacerbation of glycosuria; and in normal animals to an elevation of blood glucose and an increased liver glycogen. The important point still to be determined is the manner in which the action of these two hormones is related to each other.

This question may be approached in two ways. First, we may consider to what extent the removal of the adrenal glands reduces the action of anterior pituitary extracts, and secondly to what extent may the disturbances in the metabolism of hypophysectomized animals be corrected by the injection of the cortical hormone.

The influence of anterior pituitary extracts on the metabolism of adrenalectomized animals has been the subject of some difference of opinion. This, undoubtedly, was due to the failure to recognize the multiple nature of their action. At the present time, certain of their effects do not appear to be obliterated by removal of the adrenals, while others undoubtedly are.

The effects on metabolism that do not require the presence of the adrenals are (a) the inhibition of the action of exogenous insulin-glycotropic action (Himsworth and Scott (30)); (b) the maintenance of the muscle glycogen levels of fasted hypophysectomized rats—glycostatic action (Bennett (26), Russell and Bennett (31)); (c) the effect of anterior pituitary extracts on reducing the protein catabolism (Harrison and Long (unpublished experiments)).

On the other hand, there seems to be good evidence that (a) adrenalectomy attenuates a total pancreatic diabetes (Long and Lukens (16), Houssay and Biasotti (27b)); (b) the effect of anterior pituitary extracts in exciting acetonuria and increasing liver fat is much diminished after adrenalectomy (Fry (28), MacKay and Barnes (29)); (c) the injection of anterior pituitary extract into adrenalectomized rats maintained on sodium chloride does not cause glycosuria (Long (25)), unless the animals have been treated with cortical extract (Houssay and Biasotti (27a), cf. also *Figure 11*).

The only pituitary factor that we know will influence the adrenal cortex is the adrenotropic principle, and Bennett has shown that extracts rich in this hormone will augment the liver glycogen and blood glucose of fasting hypophysectomized rats, and suggests that this pituitary hormone has an influence on metabolism that is due to its effectiveness in stimulating the secretion of the adrenal cortical hormone. Such a finding is in keeping with the positive effects I have already described of this hormone on metabolism.

This brings us to our second consideration, the ability of cortical extracts to repair the disordered metabolism of hypophysectomized animals. That these extracts would have a marked effect was foreshadowed by the work of Baird, Cloney and Albright (32), who showed that hypophysectomized rats could be protected against the lethal effects of cold by its use.

It will be recalled that not only have fasted hypophysectomized rats a very abnormal metabolism characterized by excessively low levels of carbohydrate, but that in them the adrenal cortices have undergone marked atrophy. If the above view of the mode

of action of the cortical hormone is correct, we ought to be able to favorably influence these low carbohydrate stores, and furthermore, if an anterior pituitary factor, independent of the adrenal cortex, is also involved, then the use of this along with cortical extract should completely restore the various carbohydrate constituents of fasted hypophysectomized rats to the levels encountered in fasted normal rats. Recent experimental work has borne out this hypothesis. In the first place, hypo-

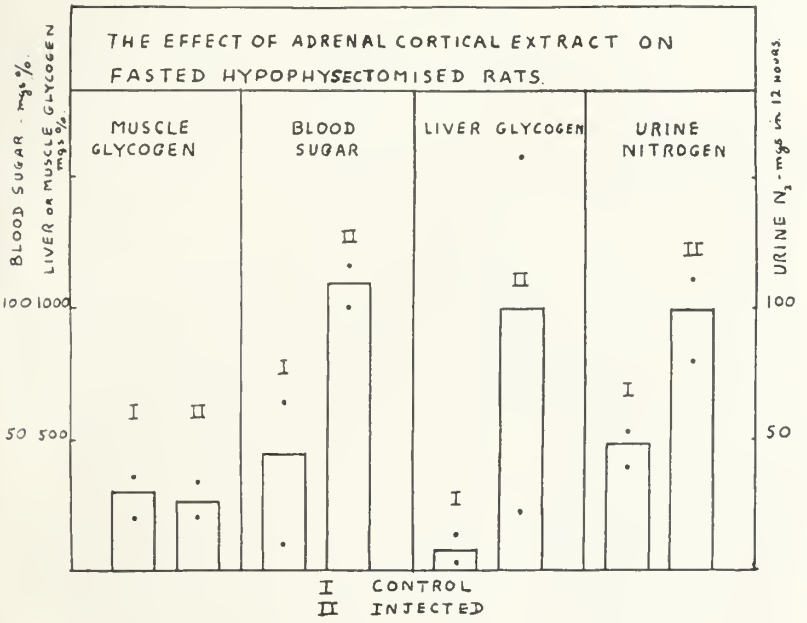


Fig. V

physectomized animals treated with either adrenotropic hormone (Bennett (22)) or with sufficient quantities of cortical hormone (Katzin and Long (21)) have an elevated blood glucose and a liver glycogen content that greatly exceeds that of normal animals (*Figure V*). The muscle glycogen, however, is only slightly increased. However, as Russell and Craig (23) have shown, if both adrenal cortical hormone and anterior pituitary extract are injected, not only does the blood glucose and liver glycogen

increase, but also the muscle glycogen, to levels above those encountered in normal fasted rats. Consequently, it may be assumed that to restore the metabolism of hypophysectomized rats to normal at least two anterior lobe factors are required, one (or more) acting independently of the adrenals and another producing its effects through its influence on the adrenal cortex. To these should also be added the thyrotropic hormone, whose presence is required to elevate the metabolic rate and to restore the rate of glucose absorption from the intestine to normal (Russell (33)).

It should also be noted (*Figure 1*) that the treatment of hypophysectomized rats with cortical extract increases the urinary nitrogen excretion and this result indicates, as it did in the normal animals, that the source of this newly formed carbohydrate is the protein stores of the tissues.

THE CO-ORDINATION OF METABOLISM BY THE ENDOCRINE GLANDS

In spite of the fact that I have emphasized the influence of the hormones on certain phases of metabolism it should not be forgotten that the ability to utilize or oxidize foodstuffs is an inherent property of the cells and that the endocrine glands through their secretion only accelerate or inhibit certain phases of these transformations.

Thus, although it has been said in the past that in the absence of insulin the organism is unable to utilize glucose, a recent research has shown that the removal of the hypophysis or adrenals restores to some degree the ability to oxidize this carbohydrate. Similarly, thyroidectomy, although reducing the rate of oxidation in cells, does not completely suppress it and hypophysectomy, although greatly retarding protein synthesis, does not entirely prevent growth since regeneration of such organs as the liver still occurs after its removal.

The exact manner in which a hormone diverts the metabolism in one direction or another is still unknown. It may be that just as certain vitamins have been shown to be a part of the enzyme systems concerned with particular chemical transformations so ultimately a similar rôle will be assigned to the hormones. This is for the future to decide.

In reviewing our present concept of metabolism certain features stand out. First of all, the complexity of chemical changes that even a single compound such as glucose undergoes before it is converted into CO_2 and H_2O. A few of the enzyme systems concerned in these transformations have been identified, but many are still unknown. Interference with a single phase of these changes may theoretically inhibit the complete oxidation of glucose.

If the inhibition of glucose catabolism occurs, as it does in vitamin B_1 deficiency, at a three carbon compound stage, then the further utilization of pyruvic and lactic acid is retarded, and it is these substances and not their mother substance, glucose, that accumulate in the body fluids and urine. This type of inhibition of carbohydrate utilization is just as dangerous to life as an inhibition of glucose utilization, yet we are not accustomed to think of them as possessing any features in common.

Secondly, the endocrine system displays a marked versatility in meeting the various circumstances to which the metabolism must adjust itself. During starvation carbohydrate utilization is reduced to a minimum by operation of the anterior pituitary and a reduction in insulin activity. At the same time, since a certain level of blood glucose is necessary for the maintenance of life an increased rate of tissue protein catabolism is established, in which process the adrenal cortex participates. Yet the excessive operation of this factor is counterbalanced by still another anterior pituitary factor that retards protein catabolism. Since the adrenal cortex is also under the control of the anterior pituitary this organ must play a major rôle in the metabolism of fasting animals, preserving the blood sugar level and regulating the catabolism of protein. As a consequence, fat which is stored in large amounts for such contingencies must furnish the bulk of the energy requirements.

In the well-fed animal the emphasis is on anabolic processes. Protein is synthesized and fat stored, and since a portion of each of these food substances yields glucose which is added to that ingested in the diet, increased quantities of insulin are required to effect its oxidation and deposition as muscle glycogen. Under these circumstances it seems probable that the activity of those

hormones that suppress carbohydrate utilization is reduced to a minimum.

Finally, provision must be made for those emergencies which require adjustments in metabolism to be made at a more rapid rate than the anterior pituitary, thyroid, or adrenal cortex can affect them. In this regard the central nervous system, with its related endocrine glands, the adrenal medulla and posterior pituitary, seems the most important. We are almost entirely ignorant of the manner in which the nervous system may influence metabolism except through its control of the secretory activity of these two endocrine organs, but we are well aware that the adrenal medulla effects a rapid elevation of the blood sugar level and through its influence on the peripheral vascular system prevents heat loss. At the same time it increases heat production by metabolic changes not entirely understood. The posterior pituitary is concerned with the regulation of that most important constituent of the body—water. The water and salt metabolism are also influenced by the adrenal cortex, but the precise relationship between this and its effect on protein and carbohydrate metabolism is not clearly defined at present.

Figure VI is an attempt to include within a schematic diagram the major interconversions of protein, fat and carbohydrate, and also to indicate our present understanding of the relation of certain hormones to these processes. This newer knowledge of the manner in which metabolism is controlled by the endocrine system is largely, if not entirely, based on experimental work. Its value in the solution of the problems of diabetes mellitus and other disorders of metabolism in man is at the present time unknown; but it can hardly fail to have a far reaching influence. I am given confidence in this belief by the knowledge that in no other disease have the results of experimental work on animals been more fruitfully applied than in diabetes mellitus.

The studies from my Laboratory have been conducted with the assistance of Miss E. G. Fry, Miss H. B. Ritter, Mrs. H. C. Harrison and Mr. B. Katzin. I am indebted to them for permission to include their previously unpublished experiments. I

also wish to acknowledge the material assistance I have received from the Committee for Research in Endocrinology, National

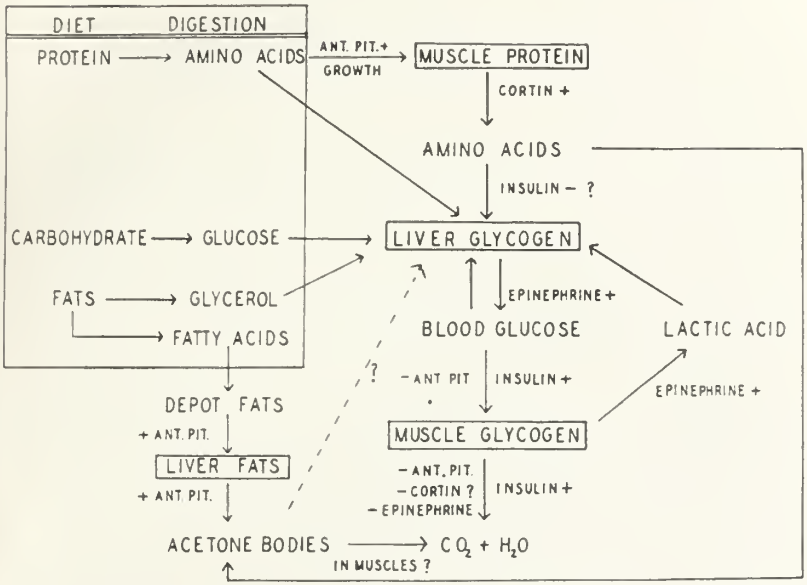


Fig. VI. Schema illustrating the principle pathways of metabolism and the influence of the various endocrine glands on them. A plus sign indicates a stimulating action, and a minus sign an inhibiting one.

Research Council, and the Fluid Research Fund of the Yale University School of Medicine for the conduct of this work.

REFERENCES

(1) Wierzuchowski, M. *J. Physiol.* **90**, 440; 1937.
(2) Ingle, D. J., Higgins, G. M., and Kendall, E. C. *Anat. Rec.* **71**, 363; 1938.
(3) Houssay, B. A. *New Eng. J. Med.* **214**, 913, 961, 971, 1023, 1086, 1128, 1137; 1936.
(4) Young, F. G. *Lancet*, **2**, 372; 1937.
(5) Campbell, J., and Best, C. H. *Lancet*, **1**, 1444; 1938.
(6) Dohan, F. C., and Lukens, F. D. W. *Am. J. Physiol.* **125**, 188; 1939.
(7) Richardson, K. C., and Young, F. G. *Lancet*, **1**, 1098; 1938.
(8) Houssay, B. A., and Foglia, V. G. *Rev. Soc. Argent. de Biol.* **12**, 237; 1936.

(9) Russell, J. A. *Endocrinology*, **22**, 80; 1938.
(10) Young, F. G. *Biochem. J.* **32**, 1521; 1938.
(11) Teel, H. M., and Watkins, O. *Amer. J. Physiol.* **89**, 662; 1929.
(12) Gaebler, O. H. *J. Exp. Med.* **57**, 349; 1933.
(13) Lee, M. O. *Res. Publ. Ass. Nerv. Ment. Dis.* **17**, 193; 1938.
(14) Richardson, K. C., and Young, F. G. *J. Physiol.* **91**, 352; 1937.
(15) White, P. Diabetes in Childhood and Adolescence. Phila., Lea and Febiger, 1932.
(16) Long, C. N. H., and Lukens, F. D. W. *J. Exp. Med.* **63**, 465; 1936.
(17) Shapiro, R., and Pincus, G. *Proc. Soc. Exp. Biol. & Med.* **34**, 416; 1936.
(18) Britton, S. W., and Silvette, H. *Am. J. Physiol.* **100**, 693; 1932.
(19) Katzin, B., and Long, C. N. H. *Am. J. Physiol.* **123**, 113; 1938.
(20) (a) Russell, J. A., and Bennett, L. L. *Am.J. Physiol.* **118**, 196; 1937. (b) Russell, J. A. *Ibid.* **121**, 755; 1938.
(21) Long, C. N. H., and Katzin, B. *Proc. Soc. Exp. Biol. & Med.* **38**, 516; 1938.
(22) Bennett, L. L. *Proc. Soc. Exp. Biol. & Med.* **37**, 50; 1937.
(23) Russell, J. A., and Craig, J. M. *Proc. Soc. Exp. Biol. & Med.* **39**, 59; 1938.
(24) Lukens, F. D. W., and Dohan, F. C. *Endocrinology*, **22**, 51; 1938.
(25) Long, C. N. H. *Medicine*, **16**, 215; 1937.
(26) Bennett, L. L. *Endocrinology*, **22**, 193; 1938.
(27) Houssay, B. A., and Biasotti, A. (a) *Rev. Soc. Arg. de Biol.* **14**, no. 5 (August), 308; 1938. (b) *Ibid.* **12**, 104; 1936.
(28) Fry, E. G. *Endocrinology*, **21**, 283; 1937.
(29) MacKay, E. M., and Barnes, R. H. *Am. J. Physiol.* **118**, 184; 1937.
(30) Himsworth, H. P., and Scott, D. B. McN. *J. Physiol.* **92**, 183; 1938.
(31) Russell, J. A., and Bennett, L. L. *Proc. Soc. Exp. Biol. & Med.* **34**, 406; 1936.
(32) Baird, P. C., Jr., Cloney, E., and Albright, F. *Am. J. Physiol.* **104**, 489; 1933.
(33) Russell, J. A. *Proc. Soc. Exp. Biol. & Med.* **37**, 569; 1937.

Proceedings of the Sections

SECTION ON GENERAL MEDICINE

Regular Meeting, January 23, 1939

The Treponemacidal Activity of Arsphenamine and Neoarsphenamine in Vitro, with Special Reference to Citrated Blood, and a Suggested Method for the Prevention of Transfusion Syphilis. Clara C. Kast,* Charles W. Peterson,* and John A. Kolmer, M.D. (*Abstract below.*)

Achlorhydria in the Leukemias. Clara L. Davis,* M.D. (*Abstract below.*)

A Correlation Study between Retinal Vascular Changes, Electrocardiographic Alterations and Radiological Heart Size in Essential Hypertension. Hugo Roesler,* M.D., Glen G. Gibson,* M.D., and Raymond Hussey,* M.D. (*Abstract below.*)

The Clinical Use of Urginin (Squill), and a Comparison of Its Action with That of Digitalis. Joseph B. Vander Veer, M.D., William D. Stroud, M.D., and Joseph C. Edwards,* M.D. (*Abstract below.*)

Abstracts

The Treponemacidal Activity of Arsphenamine and Neoarsphenamine in Vitro, with Special Reference to Citrated Blood, and a Suggested Method for the Prevention of Transfusion Syphilis.† Clara C. Kast, Charles W. Peterson, and John A. Kolmer, M.D.

Arsphenamine (disodium) produced total or marked loss of motility of virulent *Treponema pallidum* in vitro in dilution as high as 1:40,960 in saline solution and in 1:20,480 in serum after an exposure of 15 minutes at room temperature; after an exposure

* *By invitation.*

† From the Research Institute of Cutaneous Medicine, Philadelphia.

of 30 to 60 minutes total or marked immobilization occurred in solutions as high as 1:163,840 in both saline and serum.

Neoarsphenamine produced total or marked loss of motility in dilutions as high as 1:20,480 in saline solution and 1:5120 in serum in 15 minutes, and in dilution as high as 1:163,840 in both saline solution and serum after an exposure of 30 to 60 minutes at room temperature.

Final dilutions of arsphenamine (disodium) as high as 1:20,480 in citrated blood were completely treponemacidal in rabbit inoculation tests (testicular), and neoarsphenamine in dilutions as high as 1:40,960 after an exposure of 15 minutes at room temperature.

By intravenous inoculation of rabbits arsphenamine (disodium) was found completely treponemacidal in dilutions as high as 1:40,960, and neoarsphenamine as high as 1:20,480 (higher dilutions not being tested) after an exposure of 15 minutes at room temperature.

No toxic effects were observed in rats following the intravenous injection of 0.5 to 2.0 cc. of a 1:2560 solution of arsphenamine (disodium) in citrated human blood per 100 grams of weight, and apparently no toxic effects followed the intravenous injection of similar amounts of a 1:1280 solution of neoarsphenamine in citrated human blood. Human beings have been transfused with 300 cc. of 1:1000 to 1:3000 solutions of neoarsphenamine in citrated blood and with 300 to 400 cc. of 1:10,000 solutions of disodium arsphenamine and neoarsphenamine in citrated blood with no toxic or ill effects whatsoever due to the compounds. On this basis, it is advised that either compound be added to citrated human blood in final dilution of 1:10,000 for treponemacidal effects, whenever syphilis of the donor is suspected or known to be present, as a means for the prevention of transfusion syphilis. For this purpose, neoarsphenamine is preferred, 0.1 gm. being dissolved in 10 cc. of sterile water, 1 cc. of the solution then being added to each 100 cc. of citrated blood. The blood should then stand for 15 minutes, at room temperature, before it is used for transfusion.

Achlorhydria in the Leukemias. Clara L. Davis, M.D.

Twenty cases of chronic lymphatic and myelogenous leukemia were studied (1) to investigate the incidence of true achlorhydria (2) to canvass the old concept of Leukanemia of Leube in the light of Castle's conditioned deficiency hypothesis as follows: (a) to find out if a pernicious type of anemia occurs in association with leukemia (b) to investigate the influence of liver extract therapy on such manifestations.

Histamine gastric analyses were performed. Parenteral liver therapy was administered to all achlorhydrics exhibiting severe anemia (5 in all), and the reticulocyte response was noted.

Three of these exhibited macrocytic anemia and two microcytic. There was no significant reticulocyte response to liver therapy. Eight cases showed smooth tongue. Achlorhydria was present in seven cases (35 per cent). Leukemic infiltration of the liver was found in all of the six necropsies performed, and leukemic infiltration of the stomach was observed in only one and this patient had normal gastric acidity during life.

Conclusions: (1) Incidence of achlorhydria in this series (too small for statistical analyses) exhibits an incidence of achlorhydria (35 per cent) which is higher than "normal"; (2) no correlation between achlorhydria, glossitis, anemia and neurological disturbances in this group; (3) potent liver therapy has no effect on the associated anemia of leukemia; (4) the concept of Leukanemia (Leube) is without demonstrable basis and the term should be dropped.

A Correlation Study between Retinal Vascular Changes, Electrocardiographic Alterations and Radiological Heart Size in Essential Hypertension.‡ Hugo Roesler, M.D., Glen G. Gibson, M.D., and Raymond Hussey, M.D.

Eighty carefully selected cases of essential hypertension were studied from the viewpoint of retinal vascular changes, electrocardiographic alterations, and fifty-nine of them as to radiological

‡ From the Departments of Medicine, Ophthalmology, and Radiology, Temple University School of Medicine and Hospital, Philadelphia.

heart size, and a correlation between these criteria was carried out.

Retinal vascular changes were noted in all of the selected cases, with 88.8 per cent graded as sclerosis, hypertensive type. The electrocardiogram revealed final deflection changes in 68.8 per cent. A slight to moderate enlargement of the heart was noted in 50.8 per cent, and a marked degree in 27.1 per cent.

There is a trend towards a positive correlation between electrocardiographic alterations and the grade of the retinal arteriolar changes; between cardiac enlargement and the grade of the retinal arteriolar changes; and between electrocardiographic alterations and the degree of cardiac enlargement. This correlation was not demonstrated to be of high statistical significance.

Some of the possible causes for this incomplete correlation are discussed, among which the irregular distribution of the vascular processes and the lack of strict parallelism between the systemic and central retinal artery blood pressure are stressed.

Inasmuch as there is an inadequate correlation between the three criteria in question, it seems desirable to have in a given case of essential hypertension, an evaluation of the eyeground, electrocardiogram and heart size in addition to the more routine studies when one attempts the difficult task of making a practical prognosis for a patient who has this disease.

The Clinical Use of Urginin (Squill), and a Comparison of Its Action with That of Digitalis. Joseph B. Vander Veer, M.D., William D. Stroud, M.D., and Joseph C. Edwards, M.D.

Squill is one of the oldest of known remedies. Over a period of many centuries its emetic and diuretic actions have been known. The present-day interest in the drug is due to the recent isolation of cardioactive glucosides of squill which are now available for clinical use.

Using the product "urginin" (a mixture of approximately equal parts of two of the active glucosides of squill), we have studied the effect of this drug in 42 patients with cardiovascular disease. These comprised two groups of cases: the first con-

taining 16 patients who were hospitalized because of congestive heart failure and who had previously received no preparation of digitalis; and a second group of 26 patients who had been previously well controlled with various preparations of digitalis for periods of time up to 6 years.

The beneficial and toxic effects of this drug were quite similar to those of digitalis, as was the effect on the electrocardiogram. Clinically, however, it was necessary to use approximately 5 cat units of the squill preparation to produce the same effect by mouth as 1 cat unit (1½ grains) of whole digitalis leaves. The average and most frequent daily maintenance dose of urginin was found to be 1.0 mgm. daily (2 tablets of 0.5 mgm.). Slowing of the ventricular rate in auricular fibrillation seems to be as striking in urginin therapy as with digitalis. Whether or not the direct effect on the cardiac muscle is equal to that of digitalis is still not proved. Until this fact is settled it would seem wise to limit the use of this drug to those patients with cardiovascular disease who for some reason are unable to tolerate digitalis.

Regular Meeting, February 27, 1939

The Syndrome of Periodic Somnolence Associated with Polyphagia and Polydipsia. Alfred Gordon, M.D.

The Effect of Dihydrotachysterol in Parathyroid Deficiency. Edward Rose, M.D., and F. William Sunderman, M.D. (*Abstract below.*)

Further Studies of the Intracutaneous Method of Typhoid Vaccination. Louis Tuft, M.D.

The Use of Sodium Diphenyl Hydantoinate in the Treatment of Institutionalized Epileptics. George Wilson, M.D., and Kenneth S. Scott,* M.D. (*Abstract below.*)

Abstracts

The Effect of Dihydrotachysterol in Parathyroid Deficiency. Edward Rose, M.D., and F. William Sunderman, M.D.

The relationship of dihydrotachysterol to the other sterols

* *By invitation.*

derived from irradiated ergosterol is presented and the physiological action of this substance as described in the German and American literature is briefly reviewed. It has little or no anti-rachitic effect but is highly effective in producing a rise in serum calcium concentration both experimentally and clinically. In sufficient dosage it produces metastatic calcification and may cause fatal hypercalcemia. Its fundamental action appears to be similar to that of vitamin D (calciferol): i.e., an increase of calcium absorption from the gut and an increased phosphorus excretion in the urine. Variations in the speed of action and the optimal dosage of dihydrotachysterol are discussed and its clinical use in parathyroid deficiency and other conditions such as asthma, urticaria, hemophilia and peripheral circulatory disturbances is mentioned.

Studies on five patients suffering from post-thyroidectomy parathyroid insufficiency varying in duration from six months to fourteen years are reported. Studies on the concentration of serum calcium and phosphorus, serum protein and diffusible and non-diffusible fractions of the serum calcium as well as calcium balance studies were carried out before and after the administration of dihydrotachysterol to these patients.

Our experience confirms previous reports of the effectiveness of dihydrotachysterol in parathyroid deficiency and indicates that both the diffusible and non-diffusible fractions of the serum calcium share about equally in the rise in concentration of total serum calcium which follows the administration of dihydrotachysterol. Insofar as they permit conclusions to be reached, our study of urinary and fecal calcium excretion likewise supports previous opinion concerning the effect of dihydrotachysterol in increasing urinary calcium at the expense of fecal calcium.

The Use of Sodium Diphenyl Hydantoinate in the Treatment of Institutionalized Epileptics. George Wilson, M.D., and Kenneth S. Scott, M.D.

1. In this limited number of cases, an attempt has been made to show that the effectiveness of sodium diphenyl hydantoinate in the control of convulsive seizures in a group of institutionalized

patients is approximately that claimed by the original investigators in their larger groups of cases.

2. A group of twelve patients showed a marked diminution in frequency of attacks under this drug, becoming definitely quiescent in six instances. This group had not been proved to be resistant to other forms of anticonvulsant therapy.

3. In patients previously treated with phenobarbital in fairly large dosage, there has been definite improvement under sodium diphenyl hydantoinate with apparent quiescence in several cases and partial abatement in others; in some no improvement has occurred. In general this known resistant group probably showed less response than might a group picked at random from our hospital files. It should again be emphasized that this is an early report on this group and an improvement might be expected in many patients still not up to maximum dosage.

Regular Meeting, March 27, 1939

Periarteritis Nodosa, with Necropsy Findings. Abraham Trasoff,* M.D., and Maxwell Scarf,* M.D. (*Abstract below.*)

Experience with Sulfapyridine at the Pennsylvania Hospital. Tracy D. Cuttle,* M.D., Garfield G. Duncan, M.D., and Everett Evans,* M.D. (*Abstract below.*)

Clinical Experience with Sulfapyridine in Pneumococcic and Gonococcic Infections. D. Sergeant Pepper,* M.D. (*Abstract below.*)

Mortality of Pneumococcic Pneumonia at the Philadelphia General Hospital, 1938–1939. Leon Schwartz,* M.D., and Harrison F. Flippin, M.D. (*Abstract below.*)

Abstracts

Periarteritis Nodosa, with Necropsy Findings. Abraham Trasoff, M.D., and Maxwell Scarf, M.D.

An elderly woman who suffered from bronchial asthma for years was studied in Dr. Trasoff's ward at the Mount Sinai Hospital. The clinical symptoms and signs consisted of poly-

* *By invitation.*

neuritis of both legs, emaciation, fever, evidence of pulmonary fibrosis and arteriosclerosis. Laboratory findings were leucocytosis, eosinophilia, rapid sedimentation rate and RBC in the urine. The possibility of pulmonary tuberculosis, malignancy, avitaminosis, cardiovascular disease and hyperthyroidism were considered. Complete studies including serology, chemistry, sputum-examination, BMR, EKG, x-ray of the gastro-intestinal and genito-urinary tracts were all negative. The only positive findings were the presence of tuberculosis of both upper lobes and bronchiectasis.

A biopsy of an inguinal gland and muscle tissue was negative.

The patient died five weeks after admission. Autopsy revealed necrotizing polyarteritis involving practically every organ in the body.

The case is reported for the purpose of stressing the possible relation of allergy to the etiology of polyarteritis nodosa and urging a more frequent intravitam diagnosis.

Experience with Sulfapyridine at the Pennsylvania Hospital. Tracy D. Cuttle, M.D., Garfield G. Duncan, M.D., and Everett Evans, M.D.

Fifty patients from the medical services of the Pennsylvania Hospital and two patients from other hospitals were treated with sulfapyridine during the course of this investigation.

Forty-three of these patients were suffering from pneumococcal pneumonia. The only death occurred in a man, aged 77 years, suffering from pneumonia involving the entire right lung in which the Type III pneumococcus was the causative organism.

A colored woman, aged 49 years, suffering from pneumococcal meningitis, Type XXV, with bacteremia and clinical evidence of endocarditis recovered following treatment with sulfapyridine.

Three young men with meningococcal meningitis made dramatic recoveries following treatment with sulfapyridine. This is, to the best of our knowledge, the first report of the clinical use of sulfapyridine as the only therapeutic agent in the treatment of meningococcal meningitis.

The disappointing failures in the treatment of empyema are

in contrast to the dramatic results observed in these cases of meningitis. Five patients suffering from pneumococcal empyema were treated with sulfapyridine. High concentrations of the drug were obtained in the empyema fluid without any appreciable effect on the cultural characteristics of the organisms or on the clinical course of the disease. Surgical drainage was required in all five cases.

Seventy-one cases of Type I pneumococcal pneumonia, comprising our own and those reported in medical writings, have been treated with sulfapyridine. The results are compared with those obtained in 100 cases in which type specific anti-pneumococcus serum was given and 100 cases in which neither sulfapyridine nor serum was given. The mortality following treatment with sulfapyridine was 4 per cent as compared with 13 per cent following treatment with type specific serum and 24 per cent in those patients who had received non-specific treatment only.

Vomiting was the most distressing symptom during the use of the drug. The simultaneous administration of sulfapyridine with alkalis, acids, or colloidal gels, failed to alleviate this symptom.

Sulfapyridine is a toxic drug and should be used only under careful supervision and in those conditions in which its worth has been proved by properly controlled therapeutic trials.

Clinical Experience with Sulfapyridine in Pneumococcic and Gonococcic Infections. D. Sergeant Pepper, M.D.

A report of the clinical results in 300 cases of pneumonia treated with sulfapyridine. One hundred of these cases have already been reported in the literature. The diagnosis in all cases was definitely established by clinical history and physical examination and substantiated in the great majority of cases by x-ray. In every case a typed pneumococcus was obtained from sputum, blood culture or by lung puncture. The dosage employed, in the majority of cases, was a 2-gram initial dose followed by 1 gram every fourth hour until a total of 25 grams had been given.

Results: In the 300 cases there were 23 deaths, a mortality of 7.6 per cent. One hundred and forty-two of the cases fell in Types I, II and III with a mortality of 11.2 per cent. There were 32 cases with positive blood culture with 7 deaths, a mortality of 21.8 per cent.

The most common toxic reaction, nausea and vomiting, occurred in 170 of the patients. Two cases each of dermatitis and acute hemolytic anemia occurred and one of leucopenia.

The toxic effects of the drug appear to be more common in the ambulatory patient. Sixty-four male patients with acute or chronic gonorrheal urethritis were given 3 grams of sulfapyridine daily for four days, then 2 grams daily for from 6 to 10 days. The results showed 80 per cent cure in those that completed the course of treatment. In this smaller group with lowered dosage there were only two cases of vomiting but two cases of dermatitis and six patients who returned to the dispensary with pyrexia.

In summary, sulfapyridine in our hands has been a very valuable therapeutic agent in the treatment of pneumonia. Its usefulness in the treatment of gonorrheal urethritis would appear to lie in the evaluation of its ultimate toxicity.

Mortality of Pneumococcic Pneumonia at the Philadelphia General Hospital, 1938–1939. Leon Schwartz, M.D., and Harrison F. Flippin, M.D.

A total of 218 cases of adult, typed, pneumococcal pneumonia were treated at the Philadelphia General Hospital from August 1, 1938, to March 1, 1939. Of this number, 36 received specific antisera, with a mortality rate of 8.4 per cent. One hundred and thirty-five patients were treated with sulfapyridine, with a mortality rate of 8.1 per cent. Thirty-five patients received non-specific therapy, with a 28.1 per cent mortality. A further comparison is made in patients having Type I and Type II pneumonias. In the Type I series there was a mortality rate of 10 per cent in the serum-treated cases, 3.3 per cent in the sulfapyridine-treated cases, and 50 per cent in the non-specific group. In the Type II cases there was a mortality of 20 per cent among

those receiving serum, and a mortality of 7.7 per cent in the sulfapyridine-treated cases. There were no deaths in the non-specific group.

SECTION ON MEDICAL HISTORY

Regular Meeting, February 13, 1939

A Symposium on the Cellular Theory

The Early History of the Discovery of the Cell. William H. F. Addison, M.D. (*Abstract below.*)

Rudolf Virchow and Cellular Pathology. Edward B. Krumbhaar, M.D. (*Abstract below.*)

The History of the Chemistry of the Cell. J. Harold Austin, M.D. (*Abstract below.*)

The Division and Development of Eggs without Nuclei. Ethel Browne Harvey,* Ph.D. (*Abstract below.*)

Abstracts

The Early History of the Discovery of the Cell. William H. F. Addison, M.D.

The term 'cell' in its biological sense was first applied by Robert Hooke in 1665; while other terms, such as utricles, bladders, little boxes and globules were used by other microscopists, Grew, Malpighi, and Leeuwenhoek. The part of the cell which Hooke described was merely its wall as seen in a plant tissue, but gradually the contents of the little boxes became recognized as the living cell. To this soft living substance the term 'sarcode' was applied by Dujardin in 1835, and 'protoplasm' by Purkinje in 1839–40. The study of cells in the first third of the 19th century was much advanced by the invention of achromatic lenses, and it was the use of these which showed the similarities of plant and animal cells and led to the enunciation of the cell doctrine by Schleiden (1838) and Schwann (1839). These two showed that cells are the structural units of organisms and are practically universally present; that they exist in a limited variety of forms and are essentially the same in plants

* *By invitation.*

and animals; that non-cellular elements are all cell products. They failed in the explanation of cell formation, but many years were to pass before mitosis was understood, and this should not detract from their reputation.

Rudolf Virchow and Cellular Pathology. Edward B. Krumbhaar, M.D.

Before the time of Virchow investigations of the cell had application chiefly to normal anatomy. In 1838, the year in which Schleiden's paper on phytogenesis appeared and the year preceding that in which Virchow matriculated in medicine at the University of Berlin, Johannes Müller saw clearly recognizable cells from various kinds of tumors and recognized that "the cell is by far the most frequent element of morbid growth." Nevertheless, he appears not to have grasped the significance or basic relationship of the cells to the disease. Everard Home's picture of "lymph globules" is perhaps the earliest illustration of cells in cancer, but Home, also, revealed no comprehension of their rôle in tumor development. Vogel (1843) and Lebert (1845) in their respective atlases show, however, that by the time Virchow was concluding his first major investigations, the rôle of cells in diseased structures was already receiving attention.

In 1845 Virchow identified leukemia as being due to the already-known colorless corpuscles of the blood; in 1846 he began his most important series of publications on embolism and thrombosis. There followed discoveries and concepts too numerous to be mentioned here—cloudy swelling, fatty infiltration and degeneration, the amyloid nature of "lardaceous degeneration," agenesis, heterotopia, ochronosis are but a few of his concepts and terms that we commonly use today. The great achievement of his codifying work, the "Cellular Pathology" (1858), was its generalization that the cell and its activity form the very basis of life, diseased as well as normal. The concept *omnis cellula e cellula*, furthermore, though anticipated by Goodsir and by Barry, became established in Virchow's well-known phrase.

Like other great men before and after him, Virchow had his "blind spots" in observation and deduction. In the histology

of neoplasms, for instance, a field which perhaps owed most of all to the cellular theory, he must yield place to the Danish pathologist Hannover, who visualized (1843) a connection between epithelium and carcinoma and, indeed, coined the term *epithelioma*; to Remak, who demonstrated (1852) without question that cancer, even deep in the tissues, developed from the epithelial layer; to Waldeyer, who extended (1867) Virchow's embolic theory to metastases in cancer. He overemphasized the importance of the cell in inflammation, maintaining, for instance, that a single cell became inflamed and that fibrinous exudate was a local cell product.

Virchow well recognized, contrary to the opinion of some of his modern critics, the importance of pathological physiology, as is shown by the title of his journal, *Archiv für pathologische Anatomie und Physiologie und für klinische Medizin*, and his reference, in its first volume, to pathological physiology as the very "citadel of scientific medicine, of which pathological anatomy and the clinic are only out-works." From his time on, microscopic examination of the cell and its surroundings became an indispensable part of the study of the disease process. No one today would regard the cell as the ultimate item in vital activity; yet it still remains the basic unit on which studies of normal and diseased form and function must be based. Virchow's "Cellular Pathology" should be placed with Vesalius' "Fabrica," Harvey's "De Motu Cordis," and Morgagni's "De Sedibus" as the greatest tetrad of medical books since Hippocrates.

The History of the Chemistry of the Cell. J. Harold Austin, M.D.

The development of knowledge concerning the chemistry of the cell was limited throughout the nineteenth century by the immature state of organic chemistry and the late origin of physical chemistry, which had its inception after the work of Willard Gibbs about 1875. The tetravalence of carbon was not established by Kekule until 1858, and it was in 1865 that he formulated the structure of the benzene ring.

Chemical technique during the nineteenth century made possible elementary analysis of organic material and the recog-

nition of such classes of matter as albumin, globulin, nucleoprotein, lecithin, cholesterol, cellulose, certain sugars, dextrins, and starch. The early concepts of tissue metabolism were established; some of the enzymes of the digestive juices were discovered.

Fermentation induced by cells was attributed, however, to the total activity of the cell rather than to definite intracellular enzymes. Our present concept of the enzyme belongs to the present century.

Exosmosis and endosmosis had been studied by Dutrochet as early as 1827 to 1835; but the concept of osmotic equilibrium had to await formulation by van't Hoff in 1887; and the important significance of ions in biological phenomena became apparent only about the beginning of the present century.

Our concepts of protein structure date from the work of Emil Fischer and arose almost entirely within the present century. Our knowledge of physical chemistry of proteins followed Hardy's discovery of the isoelectric point in 1905.

Chemistry furnished the stains, which facilitated histological studies from 1871 onward; but chemical concepts respecting the cell were not conspicuously clarified by this addition to histological technique.

Throughout the period when the cell doctrine was becoming established, from 1840 to 1900, chemistry was not sufficiently developed to contribute greatly to the cell concept. It is almost entirely within the present century that the major contributions of chemistry to the comprehension of intracellular mechanisms have been made. These advances in knowledge, however, are essentially unrelated to the cell doctrine, as such. It is possible, indeed, that deeper insight into intracellular chemistry will direct attention to other levels of organization rather than to that of the cell.

Division and Development of Eggs without Nuclei. Ethel Browne Harvey, Ph.D.

The development of an egg without any nuclei results from a combination of parthenogenesis and merogony. In parthenogenesis, the egg is artificially activated and the male

nucleus is lacking. In merogony, a part of an egg from which the nucleus has been removed is fertilized and the egg develops without the female nucleus. In parthenogenetic merogony, a part of an egg from which the nucleus has been removed is artificially activated, and the egg develops without any nucleus at all, either male or female. This is of interest because the nucleus contains the chromosomes and genes which are generally conceded to carry the hereditary qualities.

Parts of eggs without nuclei are obtained by centrifuging. When sea urchin eggs (Arbacia punctulata) are centrifuged for three minutes at 10,000 × gravity in a sugar solution of the same density as themselves, they stratify and break into two almost equal halves; by further centrifuging, the halves break into quarters. The nucleus always goes to the light pole, so that the heavier halves and quarters are always non-nucleate. When these non-nucleate fractions are treated with hypertonic sea water, they divide and develop, quite like the normal nucleate eggs. Some of these non-nucleate eggs have by successive cleavages developed into blastulae of some 500 cells, and several have lived for four weeks.

The internal phenomena accompanying cell division are just like those occurring in nucleate eggs, except that there are no chromosomes; the cleavage plane comes in between two well-formed asters.

Many experiments have been carried on in an effort to obtain further development of non-nucleate eggs beyond the blastula, but, so far, without success. Cell division and early development take place without nuclei of any sort, but it may be that nuclei are necessary for later development.

SECTION ON OPHTHALMOLOGY†

Regular Meeting, January 19, 1939

FINAL OCULAR RESULTS IN A CASE OF ANTERIOR, SUPERIOR POLIOMYELITIS TWENTY-SEVEN YEARS AFTER THE ACUTE ATTACK. Edward A. Shumway, M.D.

† The proceedings of this Section are abstracted in the *American Journal of Ophthalmology* and the *Archives of Ophthalmology*.

Adie's Syndrome: A Report of a Case. Harold G. Scheie,* M.D.

Clinical Significance of the Various Types of Eye Movements. Alfred Bielschowsky,* M.D.

Regular Meeting, February 16, 1939

An Additional Report on Vernal Conjunctivitis. Louis Lehrfeld, M.D., and Jerome Miller,* M.D.

Some Considerations in the Management of Hypermetropia. Alfred Cowan, M.D.

A Case of Extensive Ulceration of the Cornea, Cleared by the Dessication Peritomy. Van M. Ellis,* M.D.

Three Cases of Argyll Robertson Pupil, Apparently Non-Luetic. H. Maxwell Langdon, M.D., and Van M. Ellis,* M.D.

SECTION ON OTOLARYNGOLOGY†

Regular Meeting, January 18, 1939

X-Ray Findings on the Relation of Chest Conditions to Sinus Disease. Karl Kornblum, M.D.

The Internist's Point of View. George Morris Piersol, M.D.

The Otolaryngologist's Point of View. Austin T. Smith, M.D.

Regular Meeting, February 15, 1939

Experiences with the Labyrinth Fistulization Operation in the Treatment of Deafness, with Report of Cases. Edward H. Campbell, M.D.

SECTION ON PUBLIC HEALTH, PREVENTIVE AND INDUSTRIAL MEDICINE

Regular Meeting, February 6, 1939

Sickness Insurance in Germany: Has It Been Satisfactory? F. H. Lewy,* M.D.

* *By invitation.*

† The proceedings of this Section are abstracted in the *Archives of Otolaryngology.*

The British 'Panel' System as I Saw It Last Summer: Is It Satisfactory? Louis J. Burns,* M.D.

Security against Illness and Injury in the State of Pennsylvania Today. Moses Behrend,* M.D.

* *By invitation.*

Currents and Counter-Currents in the Progress of Medicine*

By Alfred Stengel,† M.D.

Vice-President in Charge of Medical Affairs, University of Pennsylvania; Fellow and Former President of the College of Physicians of Philadelphia

I

The world of man and of human affairs is a scene of recurring change. From the beginning of known history no two ages or epochs have been alike. There have been currents and counter-currents, advance and retreat, movements now in straight lines, again in circles. Great achievements have many times been followed by recessions. Ancient cultures sometimes and in some ways have been more brilliant than more modern ones, though as a whole, man's progress has been to higher and better things. The history of medicine, second only to that of religion in its span of the centuries, is second to none in the authentic story of accomplishments which in succession reflect the conditions of life in the periods in which they occurred. Going as far back as records carved in stone or traced on scrolls or tablets give us any clues to the life and activities of man, we find undoubted evidence of his occupation with disease or injuries and of his establishing some sort of medical practice, probably largely or wholly in the priesthood. Primitive peoples throughout the world who have left no pictured or hieroglyphic records were probably in no essential way different from those of their own order with whom in their somewhat isolated situations men advanced in civilization have come in contact. The American Indian, the Bushmen, the wild men of Borneo had their medicine men, seers or whatever they may be called, and it is altogether likely that all primitive people de-

* College of Physicians Lectures for the General Public, 1938–39. Lecture I, read at the College, November 18, 1938.

† Died April 10, 1939. Dr. Stengel had corrected the galleys of this paper. [Ed.]

veloped from the same type of beginnings. The medicine men of the savages seem to have had a status of priesthood not dissimilar from the medicine men of ancient India, Mesopotamia and Egypt about whom we have more accurate knowledge.

The sacred Vedas of India, the Papyruses of Ebers (c. 1550 B.C.) and Berlin, and the records of the Old Testament all reveal the aspirations of men to ameliorate or cure disease, as well as to prevent it by an approach to hygienic methods that we sometimes fancy as quite modern.

But, as we survey all of these almost prehistoric efforts, we find them without exception based upon the conception that disease and injury are due to visitation of avenging deities or demons. As time advances and we reach the earliest periods of Greek medicine, we still find polytheism the basis for regarding diseases as due to the anger or jealousy of this or that god. The most ancient Hebrews, though commanded by their leaders or kings to give honor and obedience to but one God, Javah, were like other primitive peoples obsessed with the belief that a large number of evil spirits operated in the world, and despite their leaders often reverted to pantheistic worship and sought to placate the evil authors of disease. In later periods, however, it is clear that the monotheistic doctrine of the Jews, and of the Christians, was the strongest factor in the elimination of the demon element in medical conceptions.

But the Ghost of Banquo would not stay down and reviewing medical history we come again and again upon revivals of demon-born disease, of witch-burnings, and mysticism even to the present day. It would surprise us, but would not kindle our pride, to analyse some of our present day beliefs and to find how much of this ancient streak of aboriginal thinking still clings to us.

Such authentic data as we possess prove that the origins of medicine, as we know it in the western world, came to us from Egypt, Mesopotamia, Syria and Persia through Greece and Arabia and finally Rome. We have little knowledge of the older medicine of India and China, but in any case no important western movement from these countries has been discovered.

Among all of the earliest peoples, disease was a visitation of the wrath of gods, though often other gods were especially concerned with the healing of illness. In Egypt, Isis, Pacht and Thot were gods or semi-divinities who presided over medicine in one field or another and sometimes Kings, like Thosortes Imhotep, functioned as physicians. Despite their attributing diseases to malign influences or gods and their resort to incantations and visitations in temples, it is surprising how often certain reasonable hygienic principles in diet, baths and general modes of life were appreciated by these early people.

We need not, however, pause longer to study this first phase of medicine, about which we have at least some authentic record, but pass on to the history of the medicine of Greece from which in an essential way all our modern medicine derives.

Going back to the dawn of Grecian medicine, the age of Homer, the gods and goddesses visited their wrath or relieved suffering as punishment or reward for mortal faults or virtues—not always however without a large element of jealousy or annoyance when other gods seemed too favorably disposed toward some unhappy mortal. The upper and the nether millstone operated superbly in Homeric days. This was of course a local era of primitive medicine no different from that of other peoples.

It is customary in our modern literature to attribute the birth of medicine to a mythical personage called Aesculapius and to speak of doctors, when it does not serve the immediate purpose to call them by some harsher name, as Aesculapians. I sometimes think of this in terms of Charles Lever's Irish character who said that, "All the Irish people claim that they are descendants of the Irish Kings. Of course this is absurd, though you must admit it's a harmless foible. To be sure, in the case of my family, it's quite true." And so we go on calling ourselves Aesculapians without much caring whether this mythical semi-god was the son of Apollo and Coronis or of Apollo and Arsinoë. In the former case, we might find medical interest in the fact that Aesculapius was, according to report, rescued by a caesarean operation; in the latter case, it might not be so cheering to our

professional vanity to recall that upon Arsinoë's abandonment of her infant, he was suckled by a goat. Notwithstanding the important medical fact that this would establish the earliest record of artificial feeding, the sting of the story is that here and there one still discerns a disposition to make a goat of the medical profession.

Whether Aesculapius was a person or a myth, at all events he or his name was used to establish the first medical guild in Greece—a guild that was nine-tenths sacerdotal and one-tenth medical. The priests of Aesculapius may at least lay one claim to helping the progress of medicine, because they stimulated the founding of a group of peripatetic* lay physicians who were in no way attached to sanctuaries and visited the sick at their homes. They were in a sense the first family physicians. Though in the beginning the Asclepiadae passed on their knowledge from father to son, eventually they established schools such as those of Cnidos and Cos, the latter forever famous because from it came Hippocrates, the real founder of medicine.

Hippocrates, believed to have been born at Cos 460 B.C., the son of a midwife and an Asclepiad physician, was in respect of his extraordinary common-sense and power of observation the greatest physician of all time. Living in an age of great philosophers and worthless sacerdotal physicians, he established a medical method at once reasonable and useful, without incantations, charms and appeal to mythical powers. His method, so strangely varying from the speculation, philosophizing and metaphysical disputation prevailing among the finest philosophers of his day, and still more remote from the mythical beliefs and practices of the Asclepiads, was the first clear note in genuine medical progress. His aphorisms remain to this day high lights in sensible medicine. "Life is short, opportunity fleeting, judgment difficult, treatment easy, thought hard, but treatment after thought is proper and profitable." "The physician is the servant, not the teacher of nature." "The physician should help not harm." "In winter abundant nourishment is whole-

* The name periodeutes or itinerant physician is more appropriate.

some, in summer a more frugal diet." "Complete abstinence often acts well if the strength of the patient can in any way maintain it." "Life is short and art is long." In hygienic matters he advises one to observe well what he tolerates well, and what badly, and to manage accordingly; to labor, rest, and sleep, all in their due season; not to eat too little, nor with too absolute regularity, that deviation from the rule may not produce harm.

Hippocrates did not undertake to control the course of disease, but observed it carefully until upon its subsidence he might interfere actively when nature indicated the right time had arrived. His contemporaries blamed him for doing too little. (Men to this day are critical of medical practice that does not include the use of many remedies and the doing of many things. To observe hygienic principles and to give nature a chance seems to them the abandonment of the patient.) One of his well known aphorisms reads: "Timidity indicates incapacity; rashness is evidence of unskillfulness." Another: "Where there is love of art, there is also love toward men." He was indeed a great physician, and springing as he did at one bound from the primitive mystical medicine that possessed the world almost wholly at his time, he must be regarded as one of the extraordinary phenomena in human history. Trained in his own father's Aesculapian school of witchcraft, priestcraft, and demon-created disease, of incantations, sacrifice of animals or even man for the appeasement of the wrath of gods, he created a method of careful observation of the symptoms and course of disease, of sound and sensible inquiry into its causes, of close study of the influence of food and drink, of weather and surroundings—a method so sound in conception that it has not been improved upon to this day within the scope of the means in his possession, mainly the senses and reflection.

Some have thought there could not have been so sudden a change from primitive to enlightened medicine within the lifetime and through the activities of an individual, or perhaps even a group, if we admit the thought that the Hippocratic writings were the product of a school rather than of a single man. How-

ever it is clear that Hippocrates was brought up in his father's house in the Aesculapian school and that the immediate result of his own activities was the establishment of the rational Hippocratic method. A wise philosopher has said, "Genius is always impossible until he appears." We need not question the probability that some of his pupils wrote some of the writings that bear his name, as some of Ruben's pupils painted much of his canvasses.

In physics we are told that action and reaction are equal and in opposite directions. In the world of human affairs, whether in the sciences, in politics, literature or art, reaction has commonly been excessive. Ages of great brilliancy such as that of Pericles have been followed by periods of abysmal ignorance, and the slumber of the Dark Ages by an awakened, enlightened Renaissance. In individual cases great discoveries have been met with violent opposition at first and have been followed by premature and frequently ignorant attempts to fit them wholly unjustifiably into some sort of system or generalization, or in the case of medicine to make them the basis for new cults of cure. It was so with Harvey and his discovery of the circulation of the blood, with Galvani and his demonstration of the effect of electricity on the movements of the frog's legs, with Vesalius and his anatomical discoveries, and so it was with Hippocrates. Almost immediately following the establishment of the Hippocratic method, medicine again passed into a shadow and, though Greece possessed profound philosophers like Plato and Aristotle, the practical, reasonable and useful method of observation of Hippocrates was supplanted by metaphysical speculation and the establishment of "schools" which did little to advance the knowledge of disease. Even the investigations of Aristotle in anatomy and physiology, important as they were, had little effect on any practical medicine in his day.

And so the great introduction to a really scientific medicine based on observation went into eclipse, to be released only here and there, first among the Egyptians and later by the Grecian school of medicine in the Roman Empire, after the fall of Greece. Such medicine as Rome itself developed or possessed

was like their morals and culture—far below that of Greece even before Hippocrates, but the influence of Greek medicine imported by way of Egypt eventually flourished in Rome though it bore little useful fruit. Cults vied with one another, such as the Empirics, who acknowledged next to nothing but that which they termed experience; the Methodists, who sought to define disease in other ways than the ways of Hippocrates; the Encyclopaedists (the celebrated and voluminous Celsus at their head), who tried to codify all preceding knowledge; the Eclectics, who devoted their efforts to annihilation of the various schools and cults; and thus we come to Galen (c. 130–c. 200 A.D.), in one way at least the greatest character in the history of medicine, for he had the unbelievable record of dominating medical thought through thirteen centuries. We may perhaps find an explanation for this phenomenal history in the fact that these were centuries during which thought, when not suppressed, was almost nonexistent.

Galen was the son of an architect, from whom he received his primary instruction; later he visited a number of the seats of learning studying philosophy, natural history and medicine under the best of masters. His anatomical studies were mainly conducted at Smyrna and Alexandria. In practical medicine he was by training and nature an Hippocratist, and largely on this account, when he finally settled in Rome as a practicing physician, the envy and antagonism of the prevailing school of Methodists, ignorant and pretentious theorizers, drove him into exile and out of practice. Though recalled to Rome by Marcus Aurelius, he did not again enter into practice, but devoted his life to investigation and writing. He was an industrious student of anatomy and physiology and a most voluminous writer. Among his several hundred books some fifteen were devoted to interpretations of Hippocrates, and he must therefore be credited with keeping alive that great system through his own writings and through the Arabians of later centuries who derived their inspiration from him. Unfortunately he was not free from the prevailing fault of his period, that of philosophizing concerning the essence of life, the nature of disease and the like, and thus

mingled with his solid achievements of sound investigation a mass of fancy and superstition. The impress of his learning and genius was however so great that through a thousand years and more to doubt Galen was medical heresy. This was the more unfortunate because his anatomy, based exclusively on lower animals and sometimes inaccurate even for such animals, was at variance with the anatomy of man and thus occasioned the denunciation heaped upon Vesalius when he revealed the truth.

In the beginning of Galen's long sway the Dark Ages were close at hand and such culture or learning as survived in isolated places was submerged. During this period it is to the everlasting glory of orientals that Arabian medicine kept up a light, feeble though it may have been, preserving the medicine of Greece and saving it from destruction. Arabian medicine which flourished especially from the eighth to the twelfth centuries contributed something but not a great deal to advance of knowledge; but while Europe was plunged in intellectual darkness it was the Arabians mainly who kept intact the best features of Grecian medicine and added something of their own. Whether in the near East or in Africa and Spain, where they were dominant, some elements of culture and medical knowledge and tradition survived and their literature preserved what otherwise might have been lost. There were great characters among these Arabians, such as Avicenna, Avenzoar and Averroes and, though none of this school except perhaps Avicenna contributed much to new thought, it is to their great credit that they preserved Greek medicine and the teachings of Hippocrates and spread it over a large part of the medieval world.

Thus we see that medicine in ancient times, emerging from the barbaric beliefs of earliest peoples, was elevated almost at a single stroke by the genius of a great man to a reasonable and almost scientific practice, only to lapse again into cults of philosophizing wherein speculation and weird theorizing displaced observation and common-sense and later fell to a still lower estate in the succession of schools of pure mysticism. Finally, after five hundred years, the teachings of Hippocrates

were restored by Galen, and later, during the long period of the Dark Ages, the tradition and teachings of Greek medicine were kept alive by the writings of the Arabians.

The darkest period of medical history was that part of the Middle Ages from the downfall of the western Roman Empire to the fifteenth century. Only in widely separated and nowhere extensive areas was a semblance of Grecian medicine preserved.

But great events were stirring toward the end of the fifteenth century; the world was awaking from its age-long sleep, and a spirit of protest and reform was growing in men's minds. It would not be profitable at this time to dilate on the causes and influences that brought about the marvelous developments that ended the Middle Ages of darkness, of superstition, of brutality, and of oppression and set in motion activities that designate the period as the beginning of modern times; but without extended discussion of the point one may conjecture that two of the great influences that changed the world were the inventions of gun powder and printing. It can have been no mere coincidence that in so many human pursuits almost simultaneously great characters made their appearance and great achievements followed. It was the period in which the significant maritime discoveries of Christopher Columbus and Vasco da Gama were made; in which Michael Angelo established the Revival of Art; in which the martyred Savonarola died on the scaffold, firm in the faith of the primitive Apostles, loving God and declaring his wish for a harmonious union of reason, religion and liberty, without any new system of religious doctrines. His martyrdom, tragic as it was, led to the great Protestant Reform begun by Huss and Jerome in Bohemia, Erasmus in Holland, Wyclif in England, and ending with the greatest and most successful of them all, Martin Luther. The counter-revolution of Ignatius Loyola in establishing the Jesuit Order was in some sense a reaction but at the same time largely a movement reflecting reform and atoning for the sacrifice of Savonarola.

The world was not yet quite ready for the new philosophy of Francis Bacon or the astronomical discoveries of Galileo, but these with others born toward the end of the fifteenth century

were animated by the same awakening that stirred the first great reformers, though their own achievements appeared in the following century.

But what of medicine? Though we may admit significant discoveries such as those of the compass, clocks, gun-powder and firearms, and printing as part of the advances in the Medieval Ages, in matters medical men generally were still groping in superstition and ignorance. Such medical men as then flourished showed a strange mixture, collectively and individually, of small knowledge based on observation and Galenic doctrine and an abundance of belief in witches, demons and celestial influences. But a strange character appeared upon the scene at the end of the fifteenth century to give the first powerful impetus to revolt.

He too was one of the reformers (though in the field of medicine) but not dissimilar from those whose revolutionary activities concerned art, religion, and science. Theophrastus (Aureolus Paracelsus) Bombastus von Hohenheim, born in Switzerland the son of a physician, learned alchemy, astrology and medicine from his father. Of formal education he probably had little, but as an itinerant student and a surgeon in wars he travelled through many countries and consorted with all conditions of men—mostly of low orders. He seems to have weighed the opinions of all, high and low, and reached his own conclusions. He read few books and said that "reading never made a doctor but practice is what forms the physician." He finally became a professor at Basle and promptly affronted the medical faculty by lecturing in German instead of Latin. He admitted that he was the greatest medical genius in Germany and perhaps he was. As an illustration of his spirit of revolt he burned the works of Galen and Avicenna in his lecture room. His strength was his keen mind, the knowledge derived from extensive travel and his revolutionary spirit which made him the first to rebel against the thirteen centuries of thralldom to Galen. He seems to have been a thoroughly disagreeable fellow, but one totally unafraid and seeing the light of the new era as none of his contemporaries did. Though he could not throw off the shackles of theosophy and philosophy, he was withal a man of sound common-sense

and valued natural forces (the *vis medicatrix naturae*) as they had been esteemed by Hippocrates. Shakespeare called him the greatest physician after Galen. He introduced into medical practice mineral remedies—iron, lead, sulphur and antimony, overthrowing the Galenical system of vegetable drugs only. He merits our consideration here mainly because he represents one of the significant counter-currents in medicine, in routing blind acquiescence in all the doctrines of Galen and in paving the way for his final overthrow by Vesalius and Harvey.

A late contemporary of Paracelsus, Ambroise Paré, of humble origin, a barber and the son of a barber, and almost innocent of higher education, performed for surgery the same reforming service that Paracelsus gave to medicine, for which he is universally revered as the father of surgery. His rational methods in the treatment of wounds, in the substitution of ligatures for hot oil for the control of hemorrhage; his declaration that ground-up mummies and remedies derived from the horn of the unicorn are useless medicines, which won him the denunciation of the whole Paris Faculty—his declaration, "I dressed him, God healed him", and his publishing and teaching, as did Paracelsus, in his own language, instead of Latin, reveal the character and mind of the man and incidentally the state of the official medicine of his day.

The way however was paved by the rugged common-sense of Paracelsus and Paré for the emergence of a far greater character, Andreas Vesalius of Wesel, the father of anatomy, who by facts of observation and not by theory opposed at every turn the teachings of Galen, accepted servilely during 1300 years, and finally overthrew him altogether. This was no easy task and Vesalius suffered the denunciations of his contemporary anatomists, even of his own master Sylvius, and eventually burned his remaining writings and abandoned anatomy, though he escaped the unhappy fate of his fellow-student, Servetus, who was burned at the stake.

Within a few years, at the opening of the next century, by one of those curious reactions which exemplify the ever-recurring cross-currents of human intellectual achievement, there followed

a new set of strange cults, partly phantasy, largely alchemistic, and wholly useless which in their day occupied enough attention to cloud for a time the important common-sense doctrines of the three great characters in the medicine preceding them— Paracelsus, Paré, and Vesalius. But the pendulum will swing and there was soon to appear a still greater on the medical horizon— the man who in all justice must be regarded as the founder of scientific medicine and the originator of the true scientific medicine of this day— William Harvey.

This notable man was born in 1578 and died 1657. Though educated, medically, in the prevailing traditions at Padua, upon his return to England he was soon engaged in medical research of an entirely new order and was indeed the founder of what may be called investigative medicine, from which we have derived and continue to derive the great scientific advances that have not only distinguished medicine itself, but all of the biological sciences that were off-shoots from it. The world has esteemed him for his discovery of the circulation of the blood, but in the medical profession and among the scientists he will ever be revered as the founder of the true method of advancing science— that which rests upon investigation rather than on theorization, speculation and imagination. He discovered the truth regarding the circulation, perhaps as early as 1610, taught it in 1616, but did not publish his famous book "De motu cordis" until 1628. It may be quite possible that Shakespeare, who lived up to 1616, knew Harvey and his discovery and may have had it in mind when he caused Brutus to say at the report of Portia's death, that she was "dear to me as are the ruddy drops that visit my sad heart." Is it not a sad commentary on the medicine of his day that after the publication of Harvey's book his fellow-physicians assailed him violently for doubting Galen and his patients abandoned him as one possibly somewhat mad? This was the reaction to perhaps the greatest achievement of all medical history.

One other distinguished medical character graced English medicine in the seventeenth century—Thomas Sydenham. A century that could produce a Harvey and a Sydenham may well

be rated glorious. Born in Dorsetshire, the son of a farmer, Sydenham was educated at Oxford, Montpellier and Cambridge and became a practicing physician in London. Hippocrates was his model and he has been called the English Hippocrates. He relied on observation and trained experience, and though appreciative of the advances of anatomy and physiology, denounced the employment of these sciences in the production of hypothesis based upon pure theory. Sydenham's works throughout are eloquent examples of sound common-sense, and his descriptions of diseases vaguely known in his day give the same evidence of close bedside observation and have the same clarity as those of Hippocrates.

The eighteenth century, so distinguished in philosophy, the physical sciences and art, was both progressive and recessive in medicine. It produced a few great discoverers and scientists, such as Haller, Hunter, Auenbrugger and Jenner; but also in medical practice a galaxy of learned and brilliant men largely addicted to fads and unscientific systems of practice.

A contemporary, Boerhaave of Leyden, has been generally esteemed the greatest physician of his day and was sought by patients from all parts of the world and by pupils from every country in Europe. He has an especial interest for us because the Medical School of Edinburgh was patterned after that at Leyden dominated by Boerhaave; and in turn Morgan and Shippen brought to this country the traditions of Edinburgh, which were closely followed in the establishment of the Medical School of the University of Pennsylvania. Boerhaave was essentially a clinician, but in seeking to incorporate in his system selections from many preceding systems of practice became vague and often somewhat mystical. Though he has been rated above Sydenham, the clarity of the latter shines in comparison.

I shall not pause to trace the developments of medical progress during this period, but there is a compelling reason for reference to the medicine of the latter half of the eighteenth century, for it was then that young men of this city obtained from the outstanding teachers in Great Britain and on the European Continent the sound training that enabled them on their return

to America to found the Medical School of the University of Pennsylvania in 1765, and, with others, this College of Physicians in 1787. These young men—Morgan, Shippen, Rush and Kuhn, pupils of John and William Hunter in London, the Monros and Cullen in Edinburgh, or of Linnaeus in Sweden, Morgagni at Padua and others on the Continent—brought to their native land the highest medical cultures of Europe and left behind the pretentious, bombastic, inflated and egotistic methods of the popular and aristocratic practitioners of the day with their gold-headed canes, snuff-boxes and brilliant establishments. One wonders whether in any age the panoply of pretense and fraud have not been seductive to what have been called "the best people."

However this may be, the Hunters in London were the most forward-looking scientists in England and John Hunter, in particular, the greatest surgical leader until Lister introduced a new era; the Monros and Cullen in Edinburgh were in anatomy and medicine sound, sane and outstanding. Morgagni was the innovator of pathological anatomy (Baillie in England a generation later doing notable work) and Linnaeus, as the world knows, was the great botanist whose deep knowledge influenced not only botany but all science.

The group of young Americans who were studying in England returned before the next great milestone in medical progress was reached and quite probably knew neither the man nor that which was shortly to appear. But the world knows that Edward Jenner (born in 1749), a country physician, received information from a milk-maid that cow-pox has protective power against small-pox and made this the study of his medical life. Becoming a pupil of the great John Hunter in London, this eminent man said to him regarding his supposed discovery: "Don't think, investigate." Though his observations began before 1770 and were communicated to a leading medical authority ten years later, his first actual vaccination was done in 1796 and he first published the results of his work in 1798. What a commentary on the breathless haste of many another publication of supposed discovery!

Jenner's great discovery, checked and counter-checked by controlled observations, was the first great achievement in preventive medicine and without doubt ranks as one of the great gifts to man. The fact that in his day scores or hundreds protected by vaccination were found immune to inoculation with the virus of small-pox, and that, wherever systematically applied, vaccination has almost completely eradicated recurrences of this disease, seems not to weigh heavily with certain types of people who still support antivaccination movements. Fortunately the informed and common-sense appreciation of the whole world has prevented interference with a practice that has annihilated epidemic scourges and saved countless millions of lives.

The spirit of unrest created by the French Revolution just before and after the opening of the nineteenth century might well have delayed but did not prevent significant advances in medicine. Strange as it may appear, despite the unsettled conditions in France, the early part of the nineteenth century produced a French school of medicine of exceptional brilliancy. Perhaps the leading spirit was Corvisart, who first showed his understanding by embracing the teachings of Auenbrugger and by translating his book on percussion. Later, after he had been a pupil of Desault and Vicq d'Azyr, the physician of Marie Antoinette, he became prominent and was appointed a Professor at the Charité. Subsequently he became personal physician to Napoleon and was sometimes known as the incorruptible Corvisart because he did not hesitate to criticize even the Emperor himself. His own pupil, the distinguished Laennec, and a group of successors, Andral, Chomel, Louis, Cruveilhier and others, established a French school in the early part of the century which was highly productive and attracted pupils from every country. Among Americans, Jackson of Boston, Gerhard, Pennock, the first William Pepper, and Stillé of Philadelphia studied in Paris in the 1830's and brought back to America the sound teachings of Laennec and Louis particularly.

During the same period, however, English medicine, though less conspicuous than at the close of the last century, was by

no means unproductive. Bright, Hodgkin, and Addison were clinicians and pathologists who wrote their names indelibly in medical history while across the Irish channel a Dublin school, with Stokes, Graves, Adams and Corrigan, shone like a bright new star in the medical firmament.

America contributed to practical medicine in this period two of the greatest blessings of mankind. The discovery and introduction of general anesthesia (ether and nitrous oxide) by Long, Wells, Morton and Jackson rank with the highest achievements in the history of medicine.

From an unexpected source, a professor of anatomy, better known as a poet and writer of literature, Oliver Wendell Holmes, the world obtained another great medical contribution. His essay, "On the Contagiousness of Puerperal Fever", was published in 1843, preceding by eighteen years the more scientifically confirmed "Etiology, Nature and Prophylaxis of Puerperal Fever" of Semmelweis. These publications were so convincing that it seems strange that medical contemporaries of Semmelweis ridiculed and persecuted him for his unconventional views.

The second half of the nineteenth century was destined to become the most brilliant in achievement since the dawn of medicine's history and to lay the foundations of an undisputed science of investigative medicine. In Germany Virchow, the father of modern pathology, taught pathological anatomy but, more important still, established cellular pathology, by which the definitions of disease on a sound structural basis supplanted the shifting clinical classifications of the past. In France Claude Bernard, one of the world's great research men, founded and carried far on its road the investigative medicine which we laud so highly in present days. Yet more significant were the researches of another Frenchman of undying fame, Pasteur, primarily a chemist but eventually a medical investigator, who destroyed forever the age-long belief in spontaneous generation and proved first that fermentation is due to living organisms and later that micro-organisms are the causes of many diseases—which therefore we now call infections. About the same time, in Germany Wöhler, and later Liebig, established organic

chemistry—another great advance out of which has grown not only increased knowledge of the fundamental nature of disease, but also possiblities of treatment impossible of achievement before.

These great contributions closely following the 1850's—modern pathology, bacteriology and organic chemistry—speedily led to a bewildering advance in medicine on all fronts. The pathologists classified and differentiated diseases on a scientific basis; the bacteriologist revealed one after another the micro-organismal causes of diseases; the chemist opened the way, not so immediately productive of practical applications, to a better understanding of the mechanism of disease.

II

Having entered medicine some decades after these epoch-making achievements were accomplished and when their applications were beginning to develop, I find a thrill in recalling my own experiences in the late 1880's. We young men who were then beginning our medical studies could not well forget the bewilderment we felt and the whole world experienced at the rapid succession of achievements and discoveries in medicine.

First of all, Joseph Lister—that far-seeing British surgeon, who before any other sensed the importance of Pasteur's discovery—revolutionized surgery by methods designed to prevent wound-infection. Shall any of us of that day ever forget the operating garb and methods of some of our surgeons who refused to see the light, and the contrasting spectacle of the progressive surgeon with his sterilized white operating gown and his care of instruments and all that came in contact with the patient? It would take too long to detail what Lister's contribution to surgery has accomplished and it is such a thrilling story that no one should undertake to recount it in connection with other, even though related, themes. The discoveries in bacteriology relating to specific causes of disease came to us so thick and fast that it seemed as if each month or even each week must produce something new. Koch's discovery of the tubercle bacillus, Klebs and Löffler's of the diphtheria bacillus, Fraenkel and

Sternberg's of the pneumococcus, Kitasato's of the tetanus bacillus, Eberth's of the bacillus of typhoid, and so on to many others—all came so quickly that we young men were overwhelmed and many of our elders refused to believe. Hardly had we adjusted ourselves to these bacteriological discoveries before Laveran showed that malaria is caused by a protozoan parasite in the blood and Kartulis in Egypt proved that tropical dysentery is due to another protozoan form.

For centuries, even from ancient times in Rome, and in modern times after Leeuwenhoek saw small animalcules or organisms under his microscope, men had conceptions of some kind of micro-organismal causes of disease, but here at last was the old-time dream come true.

In all of this extraordinary advance it must be recognized that the method which Koch devised (after Pasteur's pioneer studies) made possible the culture and identification of micro-organisms and the proof of their relations as causes of disease.

An immediately practical outcome of the discovery of bacteria was the study of how they operate and what they produce in the living body. Roux and Yersin in France, and especially Behring in Germany, toward the end of the '80's discovered that bacteria produce toxins and that inoculation with toxins will produce antitoxins, and thus the whole of serum treatment, beginning with Behring's diphtheria antitoxin, was initiated.

Somewhat later an English scientist, Wright, conceived and developed the idea that the bacteria of specific diseases, if deprived of their capacity to grow and multiply by heat-destruction, nevertheless retain the capacity of developing immunity when injected into uninfected people. From this has come protective inoculation against cholera, typhoid and other diseases of man and animals.

Should it interest you to follow with me other later significant advances in medicine it would be appropriate for me to mention how like new comets in the sky Roentgen appeared with his x-rays in '95 and the Curies with their radium a few years later; how Hopkins opened up our knowledge of vitamines soon after the turn of the 20th century; how Schaudinn and Wassermann

and Ehrlich about the same time established the causation, the diagnosis and the curative treatment of syphilis; how Minkowski and Opie and Banting established our knowledge and effective treatment of diabetes; how almost at a single stroke, through the work of Whipple, Murphy and Minot, a certainly fatal disease, pernicious anemia, was converted into a curable one; how diseases of the thyroid gland, the pituitary, and other glands of internal secretion have been established as sources of many mysteries of the older days of medicine; how insulin, adrenalin, ephedrine, new anesthetics and many other really effective medical agencies have been made available to medical practice.

Advances and recessions in the history of medical progress have recurred again and again. Almost it would seem, every forward movement inevitably leads to a retrogression. The story is not unlike that of mountain climbing. The hardy mountaineer scales one ridge or peak after another, only to meet with discouragement after each ascent in finding a valley just beyond. In human endeavor in science, medicine, or civilization there are the same recurring recessions after advances and sometimes indeed the valleys have been deeper than the foothills from which progress began. The decline of medicine after Hippocrates and again in the Middle Ages amply illustrates this. Fortunately such mass movements of retrogression have not been numerous, though viewed consecutively they are to be regarded as serious episodes in human history; but there have been literally hundreds of instances which illustrate how some brilliant achievement may be followed by a reaction. A great discovery is made, some duller mind or one with acquisitive instincts conceives the idea of creating a new system or cult based upon a spurious use of what has been discovered, and forthwith a new kind of treatment or cure is created. The despair of the genuine scientist has ever been the ill-informed who seek to make immediate applications of sound discovery only half understood. Thus many a foolish or vicious cult has had its inception and birth.

Frequently, too, great advances have had a by-product of evil when the untrained and uninformed have put some new method or drug or biological product to uses never intended or to

dangerously excessive abuse. Even such glorious triumphs of medicine as anesthesia and x-ray treatment have on occasions proved harmful by giving the opportunity to the unskilled and untrained to rush in where angels fear to tread. Sound medical education and a careful scrutiny of the qualifications of all who would practice medicine is the public's only safeguard.

Among the vestigial remnants of blind primitive medical faith there still remains a belief on the part of many that there is a remedy for every known disease and that health may be bought in a pill-box. The great scientific advances of the last half century have undoubtedly made possible the alleviation and in some cases the cure of disease, but it must not be forgotten that disease, especially serious disease, frequently means structural damage from which full recovery cannot reasonably be expected. It is by this curing or failure to cure the individual case that the medical profession is commonly judged and one hears much of the short-comings of medicine and little of its real triumphs. "With all your pretended science," we are asked, "why haven't you found a cure for cancer or Bright's disease or arthritis?" Though the individual man is and will always be immediately concerned with his own disease and doctors will strive to give him the alleviation or cure which he desires, the larger interest of mankind centers in prevention. Thanks to the noble band of medical investigators we have traveled far on this difficult road. Thirty-two years ago President Eliot, at the opening of the then new Harvard Medical School, emphasized this point. Said he, "Doubtless, the treatment of sick and injured persons has substantially improved, but, nevertheless, the death-rate in our cities diminishes slowly, and the heavy economic losses which result from disease and premature death continue. Moreover, the improvement of treatment in hospitals and private practice has been accompanied by a great increase in the cost of treatment, so that the charges upon the community resulting from sickness and injuries have, within the last thirty years, rapidly mounted, and these heavy charges are, after all, incurred for the palliation of evils already suffered, and not for the prevention of such evils."

Man for centuries has been exposed to various dangers,

venomous reptiles, fierce carnivora, ravages of flights of insects and the constant presence of formidable diseases. Eliot further remarks, "For the most part, the human race has learned how to exterminate the offending creatures, or at least to limit their ravages; and where grave infectious diseases are always present, in greater or smaller degree, or frequently recur, a considerable proportion of the population becomes in some degree immune to them. Mankind is now in the face of enemies which are not localized, but which, on the contrary, are carried all over the habitable globe on the ubiquitous routes of travel and commerce. The worst of the new enemies are minute, multitudinous, and mysterious, in that their relations and connections are unknown; they infest many of the animals with which man is associated, or pass into man from the animals and plants of which he makes use.

"If civilized society is to endure under its new exposures and dangers, it is clear that the medical profession must take up with new ardor the work of preventing approaching disease in addition to the work of treating disease arrived. The profession must recognize that health is eminently a social product, just as the psychologists have recognized that the mind of a civilized man is a social product."

Presently I may be able to show you how far preventive medicine has traveled since President Eliot spoke these words.

But first may I ask what is the public conception of medicine — its objectives and uses? The answer from an overwhelming number of our fellow-men would undoubtedly come with scarcely a moment's reflection—"to restore sick people to health, to save the patient's life, to prolong it when possible, to relieve if it is not possible to cure." But is this all of medicine? Is this all that the public can see in the labors of the self-sacrificing men of medicine since the time it had any real right to be regarded as a scientific profession? Have laymen no conception that the toils of medical men have largely eliminated infant and childhood mortality and in other ways have lengthened the average span of human life from perhaps eight years in the sixteenth century to fifty-eight or sixty years today; that medicine has

wiped out, or nearly so, infections that took their toll by thousands, yes by millions, such as smallpox, typhoid fever, malaria, cholera, the plague, tuberculosis, and the infections of childhood, diphtheria, scarlet fever, and measles; that through the work of its scientific research-men it has established modern sanitation and brought about that which otherwise would be impossible—life in large cities; that it has made possible large enterprises such as making habitable countries and climates heretofore impossible for human habitation, and the construction of great avenues of commerce like the Panama Canal; that the medical contributions toward sewage disposal, food control, water purification, improved ventilation, health supervision in schools and factories, elimination of health hazards in industry, quarantine and many other safeguards, have enormously reduced disease and human misery?

It may perhaps strike a discordant note to mention the economic significance of medicine's contribution to man. Medicine always has been kept on a high plane of service to man's best interests and any economic benefits have been little emphasized. But let us for a moment reflect on one important disease—typhoid fever. Forty years ago, before the results of scientific medical investigation had pointed the way to water purification and milk control, the prevalence of this disease was enormous. I myself saw in a hospital at one time as many as sixty or eighty typhoid patients and the number throughout the country was thousands or tens of thousands. One step, based upon bacteriological discoveries, eliminated almost the whole of this enormous illness and its correspondingly enormous financial loss.

Take, further, the example of tuberculosis. A recent tabulation (1938) of the Metropolitan Life Insurance Company shows that the death rate from this disease is just a little more than one-fifth of what it was in 1900. "As a result of this remarkable decrease in death rate, about 200,000 persons will be alive on December 31, who would have succumbed during the current year, if the rate of 1900 still prevailed."

Can anyone estimate how much of patient-suffering and family misfortune the world has been spared?

Many of us can recall or have known of the ravages of yellow fever in Cuba and Central America and of its repeated invasion of our own country. Its practical elimination from all but certain wild interior and almost inaccessible regions is the fruit of the discoveries of an American Commission.

The story of malaria is peculiarly interesting. W. H. S. Jones, president of St. Catharine's College, Cambridge, has published two books, one in 1907, the other in 1909, defending the thesis that the decadence and downfall of Greece were in large measure attributable to debilitation of the people after the importation of malaria from Africa and Asia. The decay of Rome also may have been due to the same cause. The basis of his contention that malaria was actually introduced into Greece at a somewhat late period is the fact that the word more or less definitely significant of malaria appears but once in Homer and then is not found in any other writings until several centuries later; after which it or similar words appear with increasing frequency. He calls attention to the fact that as recently as 1866 the Island of Mauritius, previously free of malaria, became invaded with infinite injury to the health and character of the people.

We are all of us familiar with the history of the Panama Canal, with the complete failure of the French under de Lesseps in the 1880's and with the brilliant success under Gorgas after Laveran's discovery of the malarial parasite and Ronald Ross's demonstration of the mosquito transmission. Thousands of deaths in the French effort led to its abandonment; the sanitary regulations of Gorgas have made the Canal Zone one of the healthy spots in the world.

Have we as a people forgotten that Reed, Carroll and Agramonte discovered and proved that yellow fever is transmitted by mosquitoes; that Ronald Ross proved the mosquito transmission of malaria; that medical men from Villemin to Koch taught us the transmissibility of tuberculosis; that McCoy, Rickets, and others opened the way to understanding the transmission of diseases in our own country by insects; that Roux and Behring first showed us the possibilities of producing anti-

toxins; that Erhlich introduced chemical therapeutics (chemotherapy) as a hopeful method on a scientific basis and actually established effective cures for syphilis, trypanosomiasis, and other diseases; that in our own days and country such effective curative or useful adjuvants to cure have been discovered as insulin in diabetes, liver extract in pernicious anemia, adrenal extracts in Addison's disease, and a large number of less established biological substances in a variety of other conditions?

Is it any wonder when medical men know these things and appraise them at their true value, that our profession is somewhat restive under the criticism leveled at it by people who are ready to embrace each new cult or pretended cure-all system based on no sounder foundation than distorted use of really significant scientific discovery? The charge, and it is by no means confined to the uneducated, is often made that medical men decry this or that cult or new-fangled cure through narrowness or jealousy; but when the same type of people who make such charges hear of a promoter or a Ponzi who promises regal profits from fraudulent methods of investment, they are eloquent in denunciation.

Our laymen friends should learn that in medicine, as well as finance, common-sense still rules the world.

And finally, what of the actual practice of medicine, of the service of the physician to the patient? In the earliest days of history medicine was in the hands of the priesthood, and those who sought aid visited the temples, the Aesculapian groves, the oracles or seers. Later in the Greek period, traveling physicians, mostly of a low order of intelligence, visited the sick in their homes and even down to quite modern days the physicians have been great wanderers. Nowhere, prior to the eighteenth century, was there anything much of that relationship of the doctor to his patient with which we are so familiar, and which has elevated the doctor in the minds and hearts of his patients to as high, if not a higher, plane than that of their spiritual advisers. *Noblesse oblige* has operated powerfully and successfully to keep the ethical and moral plane of the medical profession at an equally high level. We dare not allow this fine traditional relationship

to suffer diminution or destruction, and shall, I feel sure, preserve it in all the changing conditions of these modern times. We as a profession must bring home to the public more fully than we have ever done that the greatest glory of modern medicine is not so much the service to the individual patient, however important that is to both patient and physician, as the discovery of the causes of disease, the prevention of scourges, such as I have mentioned before, and enabling men to live with increasing health and to longer average life under all of the unfavorable conditions modern civilization has brought in company with its great gifts. The proud boast has been expressed by eminent authorities that the greatest of all forces of civilization is medicine in its various fields. It has always required the coöperation of the state to carry out the measures which medicine suggested when the larger issue of prevention for a whole people was the objective; but there has been no need and there is no need of the destruction of the fine traditions of the past. There have been times when the practice of medicine was wholly individual and the state was totally inactive. These were times when quarantine, sanitation, food control, water purification were unknown, and there is little wonder that in those days life was short and full of misery. There have been other times when the state controlled the whole of medicine and such practice as existed was at the lowest level. The future requires coöperation and conservation—coöperation to secure the public assistance in carrying medicine and all that it is capable of giving to wider and higher planes; and conservation to preserve the fine traditions of one of man's noblest and most fruitful enterprises.

Clinical Teaching in America, with Some Remarks on Early Medical Schools*

By David Riesman, M.D.

Professor of Clinical Medicine, Graduate School of Medicine, and Professor of the History of Medicine, School of Medicine, University of Pennsylvania; Fellow of the College of Physicians of Philadelphia

Medical students today take for granted the incomparable opportunities for clinical or bedside study presented to them. They do not realize, in the absence of adequate historical knowledge, that this wonderful gift did not come to them without a long travail extending over many centuries. Let us therefore briefly trace its history from the beginning.

The earliest medical teaching, as is well known, was from master to pupil in the manner of the apprentice system in vogue in the various handicrafts. This method was not without merit, for the student saw disease at the bedside and learned the little medicine of his day by actual practice under his master. As a pedagogic method it was not applicable to large classes.

With the founding of the universities and the afflux of numbers of students teaching lost its touch with practice and became entirely didactic. A knowledge of the ancient texts—of Hippocrates, Galen, and Avicenna—was considered an adequate preparation for medicine. It seems strange to us today, who are accustomed to see medical books become antiquated in a few years, that almost until modern times men used as texts the works of authors who had been in their graves five hundred and even up to two thousand years. Galen, who lived in the first century A.D., Avicenna and other Arabians, who flourished in the eleventh

* Address delivered before the Library Committee of the College of Physicians and Surgeons, Columbia University, January 20, 1939.

and twelfth centuries, held absolute sway over medical teaching until nearly the end of the seventeenth century.

After the discovery of printing with movable types in the middle of the fifteenth century, the ancient texts were printed and thereby multiplied, but scarcely any original writings were added for many years. Eventually, but only sparsely before the middle of the sixteenth century, men began to set down their own thoughts without, however, discarding Galen and the Arabians. I have in my library a small handbook, a sort of vademecum, which had evidently been used as a convenient textbook to be carried in the pocket. It contains excerpts from the writings of Hippocrates, Galen, and Avicenna—the date on the title page is 1649.

Another factor retarded medical progress during the Middle Ages and for sometime afterwards, namely scholasticism. In the schools of higher learning, such as the cathedral schools and in the later universities, objective investigation of nature was almost wholly replaced by dialectical and rhetorical discussions. The medical schools did not escape the influence of the scholastic method and adopted it although the sick all about offered unequalled and untapped opportunities for studying disease.

Some of the problems with which the medical schoolmen concerned themselves seem puerile to us today. I have elsewhere[1] mentioned a few of the questions posed in examinations and for theses by medical faculties. Some of them were: Is the loud voice warm? Is air, food or drink a greater necessity? Is the necessity of death innate? Is water more healthy than wine? Is it healthy to get drunk once a month? Is woman an imperfect work of nature? Does a libertine life lead to baldness? Should literary men marry?

Nevertheless, we must not condemn the scholastic method in toto—while unproductive from the point of view of increasing factual knowledge, the exercise of the mental faculties in syllogisms and fine-spun arguments bristling with citations of the ancients sharpened men's wits and made possible, in part at least, the astounding progress of later centuries.

[1] *The Story of Medicine in the Middle Ages.* New York, Hoeber, 1935.

Clinical and bedside teaching had to wait until the middle of the sixteenth century for its birth. Quite naturally its birthplace was that greatest of all medical schools of the period, the University of Padua, revered by Shakespeare, the alma mater of Thomas Linacre, of William Harvey, of Richard Mead and of such famous Italians as Fracastoro, Cardano, Falloppio and Fabrizio d'Acquapendente. A call to Padua was deemed the highest honor in the professional world.[2]

The actual credit for inaugurating bedside teaching belongs to Giovanni Battista da Monte (Montanus) (1498–1552), who began it in the Ospedale San Francesco in 1543, a memorable date in history, for the same year saw the appearance of two epoch-making works, Vesalius' *De Fabrica Humani Corporis* and Copernicus' *De Revolutionibus Orbium Coelestium*, the first marking the beginning of modern medicine, the second the beginning of modern astronomy and cosmogony.

After da Monte's death the method for a time fell into disuse, but was revived later in the same century by Marco degli Oddi (1526–91) and Albertino Bottoni (died 1596), who took their students not only to the bedside of the patients but also to the mortuary and demonstrated by autopsy the seat of the disease and the origin of the symptoms.

Through some of the Dutch or Flemish students at Padua bedside teaching was brought to Holland, principally by Schrevelius, van Heurne and van der Straaten. But it was Hermann Boerhaave of Leyden who raised the method to a higher level than it had reached in Italy or elsewhere. Students flocked to him from all parts of the world and he became known as *Europae totius praeceptor*.[3] The Italian dramatist Goldoni made Boerhaave the central figure in a comedy, "Il Medico Olandese," which was recited for the first time during the carnival in Venice in 1756.

Boerhaave took his students into the little hospital at Leyden, consisting of two wards of six beds each, and demonstrated diagnosis and treatment. The diagnosis of course was based on the

[2] M. Ornstein, *The Rôle of Scientific Societies in the Seventeenth Century*, 3ed. Chicago, Univ. of Chicago Pr., 1938, Page 217.

[3] Albrecht von Haller called him *communis Europae magister.*

history and the surface indications, physical diagnosis being practically non-existent.

Boerhaave's pupils carried the method of bedside teaching to their homes or, as in the case of van Swieten and de Haen, to the places to which they were called.[4] For America the most significant outpost of the Boerhaavian method was Edinburgh. Edinburgh in a real sense was the daughter of Leyden. The founding of a school of medicine in the Scotch capital had been repeatedly advocated by Archibald Pitcairne, who had taught medicine at Leyden, Boerhaave and the renowed Richard Mead having been among his pupils. Finally, about 1726, a group of men, nearly all former pupils of Boerhaave, brought about what Pitcairne had so ardently desired. John Rutherford, the maternal grandfather of Sir Walter Scott, Charles Alston and Andrew Plummer, Andrew Sinclair and Alexander Monro established a medical school at Edinburgh. With the advent of William Cullen (1712 90)[5] as Professor of Medicine, the school soon rivaled and even outshone its parent, Leyden. It became the Mecca for American students largely through Cullen, who though by no means an original thinker was like his model Boerhaave a great teacher. He was virtually the first in Great Britain to give clinical lectures and he was also one of the first University teachers to lecture in English instead of in Latin (1757).[6]

It seems, however, that John Rutherford, a few years before Cullen, in 1746, had begun the practice of giving clinical lectures, which is not surprising for he had been, as I have said, a pupil

[4] van Swieten and de Haen were called to Vienna by the Empress Maria Theresa. They very soon made of the languishing Vienna school one of the greatest in the world. Another of Boerhaave's pupils was the famous Scotchman Sir John Pringle (1707–82), who was a friend of Benjamin Franklin and accompanied him on his trips to Germany and France. (J. Bennett Nolan, *Franklin in Scotland and Ireland*, Philadelphia, 1938.)

[5] Cullen was called by Benjamin West, the Anglo-American painter, the Blackstone of medicine. Cullen was proud of his medical knowledge but prouder of his ability to read Don Quixote in the original. (J. Bennett Nolan, *op. cit.*)

[6] Cullen was one of the men Benjamin Franklin met on his visit to Edinburgh. Franklin attended a meeting of the Speculative Society. The members debated the topic, "Was Brutus right in Killing Caesar?", with Lord Kanes and Principal Robinson holding the affirmative, and David Hume and Dr. Cullen the negative.

of Boerhaave in Leyden. In commencing his lectures he described his plan as follows:

> I shall examine every Patient capable of appearing before you, that no circumstance may escape you, and proceed in the following manner: 1st, Give you a history of the disease. 2ndly, Enquire into the Cause, 3rdly, Give you my Opinion how it will terminate. 4thly, lay down the indications of cure yt arise, and if any new Symptoms happen acquaint you them, that you may see how I vary my prescriptions. And 5thly, Point out the different Method of Cure. If at any time you find me deceived in giving my Judgment, you'll be so good as to excuse me, for neither do I pretend to be, nor is the Art of Physic infallible, what you can in Justice expect from me is, some accurate observations and Remarks upon Diseases.[7]

The Royal Infirmary at Edinburgh where the teaching was done, started in 1729 as a little hospital of 6 beds—it has now over 1200.

In England, unlike Scotland, the medical schools were not parts of universities but were attached to hospitals, especially in the metropolitan area of London. This close association between hospital and medical school has had a far-reaching influence upon English medicine. It made the latter more practical, less theoretical, also perhaps less scientific than was the case in the University medical schools of France and Germany.

It is an interesting historic fact that the Scotch universities in the eighteenth century granted their degrees, especially that of Doctor of Medicine, in so liberal a fashion that it became a public scandal. Adam Smith, the famous author of *An Inquiry into the Nature and Causes of the Wealth of Nations*, in reply to an inquiry from the Duke of Buccleugh and Dr. Cullen wrote a lengthy, though temperate, letter in which he condemned this practice.[8]

The case of Samuel Leeds, a "Doctor of Physik" of the University of Edinburgh, illustrates the laxity of that university in granting degrees. Leeds was so incompetent in his duties at the London Hospital that the Board of Governors insisted that he

[7] J. D. Comrie, "Boerhaave and the Early Medical School at Edinburgh," *Ned. Tijdschr. v. Geneesk.*, 1 Oct., 1938, p. 4828.

[8] Manfred S. Guttmacher, "Views of Adam Smith on Medical Education," *Bull. Johns Hopkins Hosp.*, 1930, **47**, 164–175.

must pass the examinations of the London College of Physicians if he wanted to continue in his office. He failed in his examinations ignominiously. Dr. John Fothergill, the great Quaker doctor and benefactor of American pre-revolutionary institutions, one day made a casual remark to a colleague who happened to mention Leeds, "Take care that he do no mischief." Leeds learned of this and after his dismissal from the hospital sued Fothergill. A board of arbitrators by a vote of 3 to 2 allotted him £500 damages. Fothergill thereupon investigated Leeds' record at the University of Edinburgh and found that he had not performed by himself the exercises which he had produced as his own. Furthermore, it was proved that he knew not one word of Latin or Greek, though all papers and theses were required to be written in Latin. Dr. Fothergill brought the case before the great jurist Lord Mansfield, who decided that the evidence on the part of Dr. Leeds' arbitrators was in itself sufficient to prove the illegality and injustice of their own award.

By resorting to the courts of law in a professional matter Dr. Fothergill incurred the ill-will of his colleagues to the extent that when he came up for admission to the Royal College of Physicians he was defeated by a vote of 13 to 9.

A word should be said about the Dublin School. Although maturing a little later, it took front rank in the first half of the nineteenth century as a place of clinical teaching. This preeminence it owed largely to two men—Robert J. Graves, he of Graves' disease, and William Stokes, whose name is securely enshrined in Cheyne-Stokes' breathing and Adams-Stokes' disease. Both men were incomparable bedside teachers and brought a goodly number of young Americans to Dublin by their fame.

After the middle of the eighteenth century, while an occasional student from the British colonies in America might still go to Leyden or even to Uppsala,[9] more and more wended their way to

[9] Among the Americans who studied at Leyden was William Bull of South Carolina; however, he abandoned medicine and became Lieutenant-Governor of his state. An ardent royalist during the Revolution, he left America in 1782 and lived in England. Another American pupil was John Van Buren, who became physician to the Infirmary of the Public Workhouse and House of Correction in New York City, the forerunner of Bellevue Hospital. Adam Kuhn, subsequently Professor of Botany in the University of Pennsylvania Medical School, studied in Uppsala.

Edinburgh. Among the young Americans who came to sit at the feet of William Cullen and Alexander Monro was John Morgan of Philadelphia, who received his degree of M.D. at Edinburgh in 1763. Previously he had studied for six years with John Redman, famous in the local annals of Philadelphia as the first President of the College of Physicians. As Redman had himself been a graduate of Leyden, Morgan came under the Leyden tradition from two separate sources—through his preceptor Redman and through Edinburgh, the daughter of Leyden.[10] It was quite natural therefore that he should be an admirer of Boerhaave, of whom he speaks as "The Great Boerhaave, whose example is worthy of imitation."

While in Edinburgh Morgan discussed with Cullen the advisability of establishing a medical school in the English colonies of America. Cullen was most sympathetic and encouraged Morgan. On the latter's return to America, in 1765, he proposed to the Trustees of the Academy, in a famous address printed by William Bradford, that they establish a medical school in Philadelphia. The Trustees acquiesced at once and appointed Morgan as the first Professor in the first medical school in the Colonies.[11] He was soon joined by William Shippen, Jr., and by Benjamin Rush, the latter being only twenty-four years old when he was made Professor of Chemistry.

The young Philadelphia medical school had no hospital of its own. This was not serious, for close at hand was the Pennsylvania Hospital, founded by Benjamin Franklin and Thomas Bond in 1751. In a strict sense this is the oldest hospital in the United States and still occupies its original site.

Some local enthusiasts maintain that the Philadelphia General Hospital, familiarly known as Blockley, is older. This hospital is the direct outgrowth of the ancient Almshouse founded in 1732. The Almshouse early established an infirmary for sick

[10] Henry E. Sigerist, "Boerhaave's Influence upon American Medicine," *Ned. Tijdschr. v. Geneesk.*, 1 Oct., 1938, p. 4822.

[11] At the time of the Revolution the Colonies, it was estimated, had not more than 3500 physicians, of whom only about 400 had a medical degree; all the others had been trained through the apprenticeship system (Sigerist, *op. cit.*, p. 4823).

inmates, but whether such an infirmary can rightfully be called a hospital is a question.[12]

Thomas Bond, co-founder of the Pennsylvania Hospital, was one of five physicians who were members of the Board of Trustees of the College of Philadelphia when the medical school was organized. The diplomas of the men who were graduated in the first class of the medical school, in 1768, were signed by Bond not as a member of the Faculty but as a Trustee and Lecturer in Clinical Medicine. His signature is set apart from the others. It does not appear on the diplomas granted to the four men who received the degree of Doctor of Medicine in 1771, if I may judge from the diploma that I saw, that of Jonathan Elmer.

There has been a mystery as to why Thomas Bond was not an official member of the Faculty of the medical school. Dr. William Pepper, the present Dean, has expressed to me his opinion that in all probability Thomas Bond was precluded from becoming a member of the Faculty by his holding the office of Trustee.[13]

Dr. Thomas Bond's introductory lecture to his course in clinical medicine has become famous. He says among other things:

> The Professor of the Theory & Practice of Physic [Dr. Morgan] has had the best opportunities of improvement, join'd to Genious & application, & cannot fail of giving Necessary & instructive Lessons to the Pupils.
>
> The Field this Gentleman undertakes is very Extensive, & has many difficulties which may mislead the Footsteps of an uncautioned Traveller, therefore Lectures, in which the different Parts of the Theory & Practice of Physic are Judiciously classed and systematically explain'd, will prevent many Perplexities the Student would otherwise be Embarrassed with, will unfold the Doors of Knowledge, and be of great use in directing & abridging his future Studies, Yet there is something further wanting, he must Join Examples with Study, before he can be sufficiently qualified to prescribe for the Sick; for Language & Books alone, can never give him Adequate Ideas of Disease, & the best

[12] Bellevue Hospital had a similar origin. Four years after the Philadelphia Almshouse was opened, the city of New York (1736) established a Publick Workhouse and House of Correction which also had attached to it an infirmary. This institution was the origin of Bellevue Hospital.

[13] This was a wise rule. A number of the early medical schools were wrecked through discord arising from the fact that the members of the faculty were also members of the board of trustees. Only an independent board can "hire and fire."

methods of Treating them. For which reasons Infirmaries are Justly reputed the Grand Theatres of Medical Knowledge.

There, the Clinical professor comes in to the Aid of Speculation & demonstrates the Truth of Theory by Facts: he meets his Pupils at stated times in the Hospital, And when a case presents adapted to his purpose, he asks all those Questions which lead to a certain knowledge of the Disease, & parts Affected, this he does in the most exact and particular manner, to convince the Students how many, & what minute Circumstances are often necessary to form a judgment of the Curative indications, on which, the Safety & Life of the Patient depend, from all which Circumstances and the present Symptoms, he pronounces what the Disease is, whether it is Curable or Incurable, in what manner it ought to be treated, and gives his reasons from Authority or Experience for all he says on the Occasion; and if the Disease baffles the power of Art, and the Patient falls a Sacrifice to it, he then brings his knowledge to the Test, & fixes Honour or discredit on his Reputation by exposing all the Morbid parts to View, and Demonstrates by what means it produced Death; and if perchance he finds something unsuspected, which betrays an Error in Judgment, he like a great & good Man, immediately acknowledges the mistake, and, for the benefit of survivors, points out other methods by which it might have been more happily Treated;—The latter part of this Field of Tuition is the surest method of obtaining just Ideas of Diseases. The great Boerhaave was so attentive to it, that he was not only present at the opening of Human Bodies, but frequently attended the Slaughter Houses in Leyden, to Examine the Carcases of Beasts; and being asked by a learn'd Friend, by what means he had acquired such uncommon Certainty in the Diagnostics and Prognostics of Diseases, answered by "examining dead Bodies, studying Sydenham's observations, and Bonetus's Sepulchretum Anatomicum, both which he had read ten times & each time with greater pleasure, & improvement.[14]

In a later address to The Board of Managers of the Pennsylvania Hospital, he said:

Gentlemen:—A considerable Number of hopeful students in Physic gave such attention to the Practice of the Hospital last Year, and showed such Desire of Improvement, that I, and others of my Brethren were induced to embrace several favourable Opportunities of giving them clinical observations for their Instruction, in which we pointed out the Nature, Cause and Cure of the Diseases so much to their Satisfaction, that they, and the Professors of the Physic School have requested the Lectures may be continued this Winter, which, after consulting and obtaining a Promise of Assistance from my Hospital brethren, I have promised them. The Hospital is the properest Place for doing it in, and I think such a Course would be reputable to the Institution

[14] Thomas G. Morton, assisted by Frank Woodbury, *The History of the Pennsylvania Hospital.* Rev. ed. Phila., Times Printing House, 1897. P. 463.

and answer other good Purposes; I therefore request the liberty to put up a Meteorological Apparatus in the Picture Room for keeping a Register of the Weather and an exact account of the Epidemic Diseases, thereby caused in this country. A Neat Copy of which, with an account of all the curious cases which present in the Hospital, I will annually deposit in the Library for the Perusual of Posterity. I further request you would appoint some Day this Week to see the Plan intended and give us your Opinion of it in which you will oblige.

Your respectful Humble Servt.
Thos. Bond.[15]

It would appear from a certificate issued by Dr. Bond that he began teaching at the Pennsylvania Hospital in 1763 or earlier.

This is the Certify that . . . . , son of . . . . West Jersey, entered regularly as pupil of the Pennsylvania Hospital . . . . 1763 and continued his attendance with Diligence and Application, to . . . . 1764 during which time we hope and have reason to believe he has made considerable Progress in the Knowledge of Anatomy, and the Practice of Physic and Surgery, therefore wishing Happiness and success we give from under our Hands and the seal of the Corporation, this Testimonial of our Esteem and Approbation.[16]

The form of teaching referred to in this certificate was probably more in the nature of apprentice teaching. There is no evidence of clinical lectures on patients prior to 1766.

Benjamin Rush apparently also utilized the ward-walk method of clinical instruction. This is indicated in a Journal entry of Rev. Manasseh Cutler, LL.D., July 14, 1787:

After we had taken a view of the Museum, we returned to the upper Hall, where several physicians and all the young students in Physic in the City were waiting. Dr. Rush then began his examination of the sick, attended by these gentlemen, which I judged to be between twenty and thirty. We entered the upper chamber of the sick, which is the leg of the T. It is a spacious room, finely ventilated with numerous large windows on both sides. There were two tiers of beds, with their heads toward the walls and a chair and a small table between them. The room was exceedingly clean and nice, the beds and bedding appeared to be of good quality, and the most profound silence and order were preserved upon the Doctor's entering the room. There were only women, and about forty in number. Dr. Rush makes his visits with a great deal of formality. He is attended by the attending Physician, who

[15] Morton and Woodbury, *op. cit.*, p. 469.
[16] *Ibid.*, p. 470.

gives him an account of everything material since he saw them last, and by the Apothecary of the Hospital, who minutes his Prescriptions. In every case worthy of notice, he addresses the young Physicians, points out its nature, the probable tendency, and the reason for the mode of treatment which he pursues.[17]

Although Rush must thus be credited with having given a measure of clinical instruction, his teaching in the main was by lectures. He had not freed himself from "systems," which were the bane of medicine in the eighteenth and early nineteenth centuries.[18]

New York City was behind Philadelphia in the eighteenth century both in population and in culture.[19] Nevertheless, a medical school was established in New York City in connection with King's College three years after the one in Philadelphia was founded. The New York school has the distinction of having given the first degree of Doctor of Medicine in the colonies, in 1770,[20] a year before this was conferred in Philadelphia. The Philadelphia school originally gave only the Bachelor of Medicine degree—to ten men in the first class in 1768. The Doctor's degree was not conferred until a man had had his Bachelor of Medicine degree for three years.

It is difficult to determine when clinical teaching was begun in New York City. There was no hospital until 1771, when the

[17] For the full account of this hospital visit see: William P. and Julia P. Cutler, *The Life, Journals, and Correspondence of Rev. Manasseh Cutler* (2 vols., 1888), vol. 1, pp. 253–285. The hospital concerned has been thought to be Blockley, but Dr. Robert J. Hunter (*priv. comm.*) believes it to have been the Pennsylvania Hospital.

In 1803, sixteen years after Cutler's recorded visit, Charles Caldwell "was allowed to introduce and instruct twenty, and afterwards forty students, during his *stated visits* to the medical wards [of the Philadelphia Almshouse], on the condition of his becoming responsible for their good deportment." Caldwell himself, in his autobiography, states that his was the first course of clinical lectures in the Almshouse. (Joseph Carson, *A History of the Medical Department of the University of Pennsylvania...* Phila., Lindsay & Blakiston, 1869. Page 198.)

[18] The systems, says Rush, which divide the physicians of the present day are those of Dr. Stahl, Dr. Boerhaave, Dr. Cullen and Dr. Brown. (*Sixteen Introductory Lectures...* Phila., 1811.)

[19] In 1769 New York had 21,000 inhabitants, Philadelphia approximately 30,000.

[20] The first man to receive a medical diploma in this country was one Daniel Turner, who obtained an honorary degree of Doctor of Medicine from Yale College in 1723, apparently in return for some books given to the College; hence the wags said that M.D. stood for *multa donavit.*

New York Hospital was chartered. While the rules of this hospital, adopted in the early years of the nineteenth century, provided for the appointment by the Governors of two surgeons and two physicians, "who may give clinical lectures, a permission that they reserved the right to withdraw whenever the interests of the Institution shall in their opinion require it,"—this rule was virtually a dead letter. No clinical teaching deserving the name seems to have been given before 1840.

The late Dr. Roosa[21] was in error when he said that "New York Hospital was one of the first, if not the first institution in our country to place itself open to clinical instruction." The Pennsylvania Hospital did this in 1766.

So far as I have been able to ascertain, the first bedside instruction in New York City was given in the Lying-in-Ward of Bellevue Hospital in 1804. This, however, could hardly be called clinical teaching. It seems that the first clinical lectures, in this case in surgery, were given by Willard Parker in 1841 and by William Van Buren, also in surgery, in 1849. Their example led to similar lectures in medicine. Bellevue Hospital was opened for clinical teaching in 1849.[22]

The earliest medical schools naturally arose in cities—in Philadelphia, Boston (Cambridge), New York and New Haven, and were connected with established colleges. Dartmouth, founded in 1797 by Nathan Smith, was small but it had a growing college and thriving communities in its vicinity. With the exception of Philadelphia, however, there were very few opportunities for clinical teaching. The Harvard Medical School, founded in 1782 in Cambridge, had no hospital available. In 1809 the Almshouse with its few patients came to be used by J. C. Warren and James Jackson.[23] Some instruction was also given at the Marine Hospital at Charlestown and at the Boston Dispensary. But not until the Massachusetts General Hospital was opened in 1821

[21] D. B. St. J. Roosa, "The Old New York Hospital", *Postgraduate*, 1900, **15**, 7–21.

[22] Carlisle, Robert J., *ed.*, *An Account of Bellevue Hospital, with a Catalogue of the Medical and Surgical Staff from 1736 to 1894*. New York, Publ. by the Soc. of the Alumni of Bellevue Hospital, 1893.

[23] George R. Minot, "James Jackson as a Professor of Medicine," *New Engl. J. Med.*, 1933, **208**, 254–258.

was there any clinical instruction of significance. James Jackson became the first Professor of Clinical Medicine in the Harvard Medical School, performing his duties at the Massachusetts General Hospital. Jackson at first took a few pupils to see his private patients, but after the Massachusetts General Hospital was opened he conducted daily medical visits in the hospital lasting two hours, which the students attended. Oliver Wendell Holmes speaks with great admiration of these ward visits.[24]

The course at Harvard at that time covered two years of three months each, later of four months.

The managers of the Massachusetts General Hospital did not look with much favor on bedside teaching and in May 1824 adopted the following rules: "The pupils are not to remain in the hospital longer than is absolutely necessary for the visits. They are not to converse with the patients or nurses. During operations and while in the wards they are to abstain from conversation with each other; they are not to walk about; nor in any other way to disturb either the medical officer, or the patients. In all cases, in which it will be proper for the pupils to make any personal examination of a patient, such as feeling the pulse, examining a tumour, &c. an intimation to that effect will be given them by the physician or surgeon. It must be obvious that the greatest inconveniences must arise, if such examinations were commonly made by the pupils."[25]

In 1867 women were granted the privileges of "medical visits" in separate classes and to the female wards exclusively.

The rules of the Yale Medical School in the early years did not concern themselves seriously with the general type of instruction or with bedside study but mainly, after the pompous manner of the ancient faculty of medicine in the University of Paris, with

[24] According to *The Harvard Medical School 1782–1906* (no place, printer, or date given), p. 76, the first mention of clinical lectures given in the Massachusetts General Hosptal is in 1859, when Dr. Henry I. Bowditch became Jackson Professor of Clinical Medicine. T. F. Harrington (*The Harvard Medical School.* 3 vols. New York & Chicago, Lewis, 1905) admits (vol. 2, p. 566) that in the early years of the nineteenth century both New York and Philadelphia offered clinical advantages far in excess of those available in Boston.

[25] Harrington, *op. cit.*, vol. 2, pp. 582–3.

the conduct of the students, particularly with their relationship toward their teachers. The following excerpt illustrates this:

> The Students shall confine themselves to their rooms from half an hour after breakfast in the morning, till noon, from two o'clock to five in the afternoon, and after ten o'clock at night; with the exception of such hours as are devoted to the attendance on the Lectures and prayers, or such times as they are permitted by the Professors to pursue other employments. . .
>
> Every Medical Student shall be subject to the laws and government of the Medical Institution, and shew, in speech and behaviour all proper tokens of reverence and obedience to the Faculty of the College, as well as of the Medical Institution. And if any Student shall transgress this law, by treating them, or any of them, with reviling or reproachful language; or by behaving contumaciously or contemptuously towards them, or by being guilty of any kind of contempt of their persons or authority, he may be punished by any censure, even to expulsion, as the nature and aggravations of his crime may require. . .
>
> No Student shall stake money, or other property, in any game of hazard, or play at such game at all, within the College Buildings, or within the city of New-Haven, or any Student's room, or keep cards, or any instruments of games of hazard in his chamber.[26]

The first medical school west of the Alleghenies was established in Lexington, Ky., in 1799, as a part of Transylvania University. The career of this famous University was short but romantic. While it lasted it made the little Blue Grass town a cultural oasis. A number of its medical teachers became famous in American annals. The first professor of medicine was a Virginian, Dr. Samuel Brown, who had graduated at Dickenson College and had afterwards studied in Edinburgh, David Hosack, of New York, and Ephraim McDowell, of Kentucky, being in the same class.[27]

Today, except for the splendid medical library, largely collected by Charles Caldwell on a journey through Europe in 1820, nothing remains of Transylvania but the name. The medical school of the University of Louisville is its spiritual, if not its material, inheritor.

One or two other men of the Transylvania Medical School in

[26] Walter R. Steiner, "The Evolution of Medicine in Connecticut. . .," in: *Memorial of the Centennial of the Yale Medical School.* New Haven, Yale Univ. Pr., 1915. Pages 38ff.

[27] Robert Peter, *The History of the Medical Department of Transylvania University.* Louisville, Morton, 1905. (Filson Club Publ. No. 20). A copy of this rare publication was kindly lent to me by Dr. W. O. Bullock, of Lexington, Ky.

Mr. Boyd L. Spahr, President of the Board of Trustees of Dickenson College, has

its heyday deserve to be mentioned. Elisha Bartlett, the Rhode Island Quaker, the first Mayor of the town of Lowell, Mass., a peripatetic teacher, had been professor in the medical school of Pittsfield, Mass., but was in 1841 called to Transylvania University where he taught for three years. He then went to Europe, returning to Transylvania in 1846 for another three years. After that he gave winter lectures in the medical school at Louisville, Ky., and summer lectures at Woodstock, Vt., as well as at other places. His last position was that of Professor of Medicine in the College of Physicians and Surgeons in New York, a chair he was compelled to relinquish through illness at the end of three years.

Another professor at Transylvania was John Eberle, a native of Lancaster County, Pennsylvania, who first taught at Jefferson Medical College in Philadelphia, and then in Daniel Drake's school in Cincinnati, and finally in Transylvania. While not particularly renowned as a teacher or practitioner, his textbooks on practice, on therapeutics, on diseases of children and on midwifery, gave him a nation-wide reputation.

The medical schools of the eighteenth century in America were, as I have intimated, departments of colleges or universities.[28] In the early nineteenth century another type of medical school arose, which either had no connection or only a slender one with any other educational institution. These were the so-called proprietary schools, of which a superabundance sprang up during the first seventy-five years of the last century. The earliest was that of the College of Physicians and Surgeons of New York, organized in 1807 by the local medical society with each of its one hundred and one members made a trustee under the charter.[29]

In the same year the Medical and Chirurgical Faculty of Maryland established the College of Medicine of Maryland, nucleus of the present University of that state.

---

called my attention to a lengthy account of the life of Samuel Brown in the *Dictionary of American Biography*.

[28] Frederick C. Waite, *Ann. Med. Hist.*, 1935, **7**, 242.

[29] In a sense Harvard Medical School was a proprietary school far into the nineteenth century, until after 1864. However, it was connected with Harvard College.

In 1812 the College of Physicians and Surgeons of the western district of New York was established at Fairfield, Herkimer County, N. Y. Fairfield[30] was a village of five hundred inhabitants, nine miles north of Middle Falls, New York. This college had a slender connection with Fairfield Academy. From 1816 to 1840 it graduated 609 men and had more than twice as many students. Among its graduates were Nathan S. Davis,[31] founder of the American Medical Association, Asa Gray, botanist, and Alonzo B. Palmer, founder of the Medical School of the University of Michigan. Its first president, Lyman Spalding, is generally considered the father of the U. S. Pharmacopoeia.

In 1817 each of the five New England states except Vermont had a medical school of its own. Harvard in Massachusetts, as already mentioned, was established in 1782; the New Hampshire medical institution later known as Dartmouth Medical College, in 1797; the Medical Department of Brown University in Rhode Island in 1811, and the Yale Medical Institution, founded in 1813 in Connecticut.

The village of Castleton in Vermont had less than two thousand inhabitants (1827, in the census of 1820). In this little town a medical school was established in 1818.[32] It formed a loose affiliation with the college in Middleboro, Vermont, in 1819, an affiliation that continued until 1827. Middleboro College joined in conferring degrees but had nothing to do with the choice of teachers of the medical school. There were three lecturers: Selah Gridley (1770–1826), who apparently did not have a medical degree himself, and in addition to practicing medicine kept a general store in the village. He had quite a smattering of knowledge, even of Latin and Greek. Another lecturer was Dr. Theodore Woodward (1788–1840), a nephew of Nathan Smith, founder of the New Hampshire Medical Institution, later known as Dartmouth Medical College,[33] and of the Yale Medical Institution. By a strange coincidence both Dr. Woodward and Dr.

[30] I am unable to find Fairfield in the Medical Directory at the present time.

[31] Davis was the first to introduce graded medical instruction in an American medical school—he did this in Lind University in Chicago.

[32] Frederick C. Waite, *op. cit.*

[33] The institution at Hanover was the first rural medical school in the United States.

Gridley became insane. The third lecturer was John Le Conte Cazier, a subordinate member of the board of trustees.

The Medical Department of Bowdoin College at Brunswick, Maine, was founded in 1820; the Medical Department of the University of Vermont at Burlington, in 1822; the Berkshire Medical Institution at Pittsfield, Massachusetts, in 1823. By 1824 there were eight medical schools in New England, just one-half of the sixteen in the whole United States. The year 1827 saw the birth of the Clinical School of Medicine at Woodstock, Vermont, which after some faltering became "connected with" Waterville College, now Colby, at Waterville, Maine, an institution 250 miles distant and in another state.

All of these proprietary rural medical schools have gone out of existence.

A number of similar fresh-water medical schools arose in the vast country west of the Alleghenies. Most of them were established by men who had received their medical education in whole or in part at the College of Physicians and Surgeons of the Western District of New York at Fairfield.[34] One of these schools was located at Laporte, Indiana, a town of from 1000 to 1500 inhabitants. In its brief span, 1842–1850, it had 565 students, and 127 graduates. The other schools were Franklin Medical College at St. Charles, Illinois; Illinois College Medical School, Jacksonville, Illinois; Rush Medical College, Chicago, and Rock Island Medical College, Rock Island, Illinois. Of these five only Rush Medical College survives.

Like those in the West, the proprietary rural medical schools of the East have disappeared, either through final closure under pressure or through merger. And with their disappearance ended a none-too-savory chapter in American medical history.

The length of the course of instruction in these primitive schools was sixteen weeks, the time being so arranged as to come during the part of the year when the work on the farm was less exacting, since most of the students were farmers' sons. Clinical

[34] George H. Weaver, "Beginnings of Medical Education in and near Chicago," *Proc. Inst. Med. of Chicago*, 1924–5, **5**, 174–230, and (with additional biographical sketches) *Bull. Soc. Med. Hist. of Chicago*, 1923–5, **3**, 339–470. This is a most valuable monograph.

teaching was naturally out of the question. The faculties consisted of from five to seven professors. In general the chairs were medicine, surgery, anatomy, chemistry, materia medica and therapeutics, obstetrics, and diseases of women and children. Physiology, anatomy and surgery were usually united in one chair; physiology and pathology were often placed together and sometimes with them therapeutics. The faculty list always ended with a demonstrator of anatomy, whose function it was to obtain subjects for dissection as well as to aid in the teaching of anatomy. As there were no anatomical laws, the procuring of cadavers for dissection was a precarious business. Records of riots are scattered through the history of the eighteenth and early nineteenth centuries. In Philadelphia and especially in New York the outbreaks against the dissectors were serious, in New York attended with loss of life. Scandals connected with obtaining anatomical material in due time appeared also in the West. At Cincinnati the culmination was reached when the body of John Scott Harrison, son of William Henry Harrison, was found in the dissecting room of the Medical College of Ohio.

It must be said to the credit of the American purveyors of dead bodies that they limited themselves to the robbing of graves and did not, like the Sack-em-up men in England and Scotland, murder innocent persons in order to sell their bodies to the dissectors.

Realizing as we do today the indisputable value of clinical teaching, it seems strange to us that even in the better schools clinical instruction was not favored, as may be seen in the announcement of the College of Medicine and Surgery of the University of Michigan. "Clinical instruction, it is believed, is far better imparted in the walks of private practice, especially in that section of the country where the student intends to locate himself, than can be done even in the best regulated hospital. The hasty walk through the wards of a hospital furnishes at best but a sorry substitute for the close and accurate study of cases as they occur in the professional rounds of the private practitioner."

J. Marion Sims, who was graduated in 1835 from Jefferson

Medical College, states in his fascinating autobiography that as a student he had never examined a patient. What was true of Jefferson Medical College was no doubt true of other medical schools of that period. In 1841, however, the Trustees of Jefferson announced that Drs. Dunglison, Huston and Pancoast "are medical officers of the Philadelphia Hospital, Blockley, at which during the winter session Dr. Dunglison gives clinical lectures on medicine and Dr. Pancoast on surgery."

Nevertheless, many men in the faculties of the pioneer schools realized the value of clinical instruction, of dispensaries and hospitals. Where possible they founded ambulatory clinics. In 1847 the faculty of Rush Medical College promoted the establishment of the Chicago Hospital in which during the first year eighty patients were under treatment at one time. Selected cases were used for clinical instruction.

When the American Medical Association was organized, or rather its precursor, the National Medical Association, a committee on uniform and elevated standards of requirements for the degree of M.D. reported that clinical instruction was required in 12 and not in 7 of the 19 schools reporting.

In 1851 N. S. Davis wrote: "Of 36 or 37 medical colleges only 16 were so located as to afford an opportunity for witnessing hospital or bedside instruction. Five continued the regular course of lectures less than 16 weeks, 26 for 16 to 18 weeks, two have extended their courses to a little more than five months."

To get an idea of the exaggerated value placed on textbooks, I shall quote an announcement of Chandler Burwell Chapman (1815–1877), who taught in the medical schools at Rock Island and Davenport and also gave private instruction in anatomy. "Dr. C. purchased at considerable expense, while in Paris, during the last summer, Cruveilhier's Pathological Anatomy, including the colored plates. This will prove a valuable aid to students in preparing them to distinguish post mortem appearances—even better than a residence of months in the largest hospitals of our country."

One factor in the American system of medical education in the last century that interfered seriously with bedside instruction

was the peripatetic character of the teachers. Professors would go to a medical school for three months and give an intensive course of didactic lectures and would then either migrate to another school for the same purpose or return to private practice. That explains why some of these men occupied as many as half a dozen professorships in their lifetime.[35]

Austin Flint (1812–1886) a native of Petersham, Mass., graduate of Amherst and of Harvard Medical School in 1833, taught in Buffalo Medical College 1836–1844 and 1846–1852, Rush Medical College 1844–1845, University of Louisville 1852–1856, New Orleans School of Medicine, 1859–1861, Long Island College Hospital 1861–1868, Bellevue Hospital 1861–1886. He was called the American Laennec by S. D. Gross.

John Delamater (1787–1867), who at the early age of nineteen had received a license to practice medicine from the Medical Society of Oswego County, New York, lectured first at Fairfield, then at Geneva Medical College, at the Medical School of Maine connected with Bowdoin, and the Medical School of New Hampshire connected with Dartmouth, in the University of Vermont, at the University of Willoughby at Willoughby, Ohio, and at the Medical College of Ohio at Cincinnati. When the school at Willoughby moved to Cleveland, he became Professor at Western Reserve College where he taught general pathology, diseases of women, and obstetrics for seventeen years.

Obviously such a shifting of base as is illustrated in the lives of the men I have just mentioned was bound to prevent the development of a practical type of teaching. There would be no trouble with lectures, however, for just like a preacher the medical professor could repeat them in a different place.

When I began the study of medicine the old type of lecture system was in full flower. We were lectured to from nine in the morning until six at night, although by four o'clock the saturation point had been reached and we were far too sleepy to comprehend what was said to us. There was at the University of

[35] A few held several chairs at one time in the same medical school. Thus Nathan Smith did not fill a chair but a whole settee, as Oliver Wendell Holmes expressed it, because he was professor of anatomy, surgery and chemistry, in addition to carrying on his practice.

Pennsylvania—my Alma Mater—a Professor of the Theory and Practice of Medicine and a Professor of Clinical Medicine. They both gave what were called clinical lectures in the pit of a huge amphitheater. The patient would be brought in and the several hundred students on the benches could see him, but they learned very little in a practical way from that kind of exercise. It really made no difference what ailed the patient; the professor could use him as text for almost any disease and we would be none the wiser.

Occasionally we were taken into the wards of the Philadelphia General Hospital or the University Hospital, but I cannot recall that I examined more than two or three cases in my entire course.

At the beginning of the present century, it became customary to take students into the wards of the two teaching hospitals for an hour perhaps once or twice a week. However, on one occasion a physician of the hospital withheld quinine from a malaria patient in order to study the evolutionary cycle of the malarial organism. The Board of Guardians or Managers of the Hospital, when they heard of the experiment, peremptorily withdrew the privilege the students had enjoyed. It was not until a number of years later, when a medical man became Director of Health and in charge of the Hospital, that the precious privilege was restored.

At Johns Hopkins Hospital Medical School in its formative years clinical teaching was probably at its best in this country. William Osler's profound knowledge of literature, of pathology and of practical medicine, made him the ideal bedside teacher.

In many medical schools having their own hospitals or having close affiliation with hospitals not their own, the clinical clerkship exists. Under this system, adopted first at Johns Hopkins from English hospitals,[36] the student in his last year acts in a sense as a junior interne, in medicine and in surgery. This is possible because he does not have to attend didactic lectures.

At the present time in all first class medical schools—and there are almost no others—the students have the fullest opportunities

[36] Clinical clerkships were introduced in Harvard Medical School by Dr. Edsall in 1913. (J. H. Means, "The Teaching of Medicine in the Massachusetts General Hospital." *Harvard Medical Alumni Assoc. Bulletin*, October, 1934, 1–5.)

for bedside study not only in medicine but also in surgery and in the specialties. The didactic lecture system is virtually a thing of the past. In the majority of schools only a few are given in the clinical subjects and yet a good didactic lecture by a man of large experience is of indubitable value.

An interesting pedagogic method is that prevailing in the medical school of the University of Wisconsin. In order that the student may obtain as much clinical experience as possible, he is sent as an apprentice as it were to an extramural practitioner who supervises his training for a period.

A word should be said about clinical teaching in the out-patient departments. In my opinion this has more value than many instructors and students imagine. As the time and facilities for study are limited, compared with hospital cases, it demands quicker thinking to achieve a correct diagnosis. The patients as a class are more nearly like those that come to a doctor's office. In order to derive the most from service in the out-patient department the students must be under a good teacher— alert, informed, sympathetic.

The more the student does for himself in his clinical years the better. It is one of the defects of our entire educational system that too much emphasis is placed on acquiring facts— facts are only of value after they have been digested and assimilated as knowledge. If the student digs out the facts of the case himself he will know more about the disease in the future than if he has the facts presented to him on the hospital chart or by an instructor. I have seen a goodly number of students who passed examinations with high credits but who were quite helpless at the bedside of a more or less complicated case. A good memory helps but is no substitute for synthetic thinking. One cannot however lay down any specific rules for teaching clinical or bedside medicine. In the last analysis the method is of less importance than the teacher. Nor is the quantity of teaching material of great significance. An enthusiastic teacher can do with a few patients more than an uninspired one with many. I have often said to my students, there are no uninteresting cases. It is with medical cases as with whiskey—there are no bad ones, only some are better than others.

Memoir of John H. Girvin, M.D.*

By Francis R. Packard, M.D.

By the death of John Harper Girvin the College of Physicians lost one of its most active and devoted Fellows.

Dr. Girvin was born in Philadelphia, September 17, 1869. His father, Dr. Robert M. Girvin, a graduate of Jefferson Medical College in the class of 1862, was one of the most prominent and best-loved physicians in West Philadelphia. In his day the specialities were not so sharply defined as they now are, and though he was especially interested in gynecology and obstetrics, and was for many years Physician for Diseases of Women on the staff of the Presbyterian Hospital, he had also a very large general practice. John Girvin's mother was Susan Bell Harper. She was first married, when just out of girlhood, to Courtland Saunders, who was wounded in action and died at Charlottesville, Virginia, when but twenty-one years old. Mr. Saunders was the son of Professor Ephraim Saunders, who was head of the Saunders Institute, a large school for boys in West Philadelphia. Professor Saunders closed the Institute shortly after his son's death and gave the land on which it stood to be used as the location for the Presbyterian Hospital, which was then in its birth agony. When some years after the death of her first husband Mrs. Courtland Saunders married Dr. Robert Girvin, they joined heartily in forwarding her father's efforts to aid in the success of the new Hospital.

After receiving his preliminary education at Lawrenceville Academy, New Jersey, John Girvin became a student in the Biological Department of the University of Pennsylvania, from which he graduated in 1889. He then entered the Medical Department of the University, receiving his degree of M.D. in 1892. After graduating, he had the opportunity of serving three months as an interne on the surgical service in the Presbyterian

* Read January 9, 1939.

Hospital. He then spent four months abroad. In an autobiographical sketch in one of the Class Records he states with characteristic self-effacement, "most of my time travelling, although I did take in a little medical work." On his return from abroad Dr. Girvin served for eighteen months as resident physician in the University Hospital. On the expiration of his term Dr. Charles B. Penrose gave him a position in the Gynecological Dispensary of the University. Later he became chief of the Dispensary, and Instructor in Gynecology and Demonstrator of Obstetrics in the University. Upon the death of Dr. Robert Girvin in 1900, John Girvin succeeded to his position as Physician for Diseases of Women to the Presbyterian Hospital, and four years later was given the position of Gynecologist-in-Chief to the institution. Dr. Girvin retired from undergraduate teaching after some years, but continued to serve the University as Associate Professor of Gynecology in the Graduate School.

Dr. Girvin contributed but little to the literature of the profession. He seldom read papers before medical societies, though he quite often spoke in discussion on the floor. He was a member of many medical societies, including the American College of Surgeons. Throughout his professional career he deeply regretted his inability to confine himself solely to the practice of gynecology and obstetrics. His father's death in 1900 made it incumbent on John to carry on the large general practice which had been his father's, and which he was never able to dispense with. For this reason he was never eligible for election to membership in the national societies concerned with the specialities.

Dr. Girvin's chief professional interest, beside the Presbyterian Hospital and the care of his practice, was centered in this College, of which he was elected a Fellow in 1897. From that time until the end of his life he took a deep concern in its affairs. There was no more constant attendant at its meetings and, though he seldom read a paper before it, he frequently partook in the discussions. For some years he was Clerk of the Gynecological Section of the College. On May 2, 1917, he assumed

the duties of acting Secretary of the College and served as such until February, 1919, when he was elected Secretary and continued in that capacity until January, 1934. His familiarity with all the administrative details of the College, the painstaking care which he bestowed on the duties of his office, and his wide acquaintance throughout the profession rendered his services of the greatest value. No member of the Council was more just or fearless in expressing his opinion regarding those who came before the Council as candidates for Fellowship. His Minutes of the meetings of both the Council and College were models of what such things should be.

Dr. Girvin never married. Somewhat reserved in his demeanor, he was one of the most charming companions in social intercourse with his friends. He was a very popular member of the Rittenhouse Club, and a welcome guest at dinners or other intimate social gatherings.

He died of coronary thrombosis on October 23, 1938, at his home in Philadelphia.

Dr. Girvin is survived by a brother, Mr. Charles Girvin, of Wilmington, Delaware, and a sister, Miss Helene Girvin, of Philadelphia. His mother's sister, the widow of our beloved Fellow, John H. Musser, is also living, and her son, Dr. John H. Musser, worthily sustains the professional traditions of the family in New Orleans. A daughter of Mrs. Musser is the widow of Dr. Richard M. Pearce, one of our College's most distinguished Fellows.

Memoir of Lawrence F. Flick, M.D.*

By Joseph Walsh, M.D.

Having been intimately associated with Dr. Flick over the past thirty-six years, it is a pleasure and honor to be given the opportunity of reading a short memoir of his activities before confrères who knew and appreciated the man and his work. His principal work, needless to say, was in the antituberculosis cause. His principal forte was organization, and he had the character to make what he organized not only an active-going concern, but a lasting one. This was the result of clarity of thought, a capability of bearing responsibility not only easily, but aggressively, and a talent for the sort of publicity which brought about the early and wide recognition of the new project in such a way as to arouse the interest of those it was intended to benefit.

The list of his foundations is a long one, and includes among others the Rush Hospital for Consumptives, the Pennsylvania Society for the Prevention of Tuberculosis, the Free Hospital for Poor Consumptives, the White Haven Sanatorium, the Henry Phipps Institute, and the Nurses' Training Schools for arrested cases of tuberculosis. With the Phipps Institute in February 1903 came the first modern Tuberculosis Dispensary and the first Visiting Tuberculosis Nurse in the United States. In 1904, on the request of the Director of Health, Dr. Edward Martin, he organized the Tuberculosis Department of the Philadelphia General Hospital under a special staff of physicians. He was the saviour of the Frederick Douglass Memorial Hospital, since without his aid it would have closed its doors. It was along the lines he advocated that the National Tuberculosis Association was formed, and though at the time there were more than a few who opposed his ideas, everyone was later pleased they had been adopted. He was, also, the principal instrument in bringing to

* Read January 9, 1939.

the United States the International Congress on Tuberculosis in 1908.

The Pennsylvania Society for the Prevention of Tuberculosis represented the first organized popular movement in the United States for the eradication of the disease, and since then about two thousand similar societies have arisen throughout the country, of which he may well be called the progenitor. Further, this form of organized movement proved so successful in extending the knowledge which lowered the deathrate from tuberculosis that the new societies for the prevention of heart disease are following its lines.

It was his natural flair for justifiable publicity that made the Phipps Institute internationally known in three years, and aided not only in bringing the International Congress on Tuberculosis to the United States, but with it the largest number of eminent European medical men ever seen on this Continent. The roster of names of these physicians reads like a European "Who's Who in Medicine," and if this roster were lost it would be beyond the limits of plausibility to imagine it. It is so impressive that I cannot refrain from mentioning a few of the names: Koch, the discoverer of the tubercle bacillus, and thereby the father of all tuberculosis preventive work; Philip of Edinburgh and Calmette of Lille in France, the founders of the first tuberculosis dispensaries, which have done so much toward the treatment of recognized, and the discovery of unrecognized, cases; von Pirquet, whose tuberculin reaction made possible the study of the spread of the disease; Pannwitz of Berlin, the founder and executive manager of the International Antituberculosis Association, which met in public conference once a year till the outbreak of the World War, and practically controlled the International Congress, which assembled once in three years; Arloing of France, who did so much in connection with the artificial cultivation and reactions of tubercle bacilli; Tendeloo of Holland, whom Osler put on a special pedestal for his laboratory work on the lymphatics in tuberculosis; Raw of Liverpool, who achieved a special reputation for his differentiation of the effects of human and bovine tuber-

culin in treatment, and who has recently been for many years a member of Parliament from his native city.

There were also the distinguished internists von Leube of Germany, Landouzy and Letulle of Paris, Wladimiroff and Unterberger of Russia,—the last being also physician to the Czar, Williams, Newsholme and Latham of England, Denys of Holland and Bang of Copenhagen. And I may add that the great majority came on account of the personality of Flick, and through his special invitation.

These men gave public addresses on various popular subjects connected with tuberculosis in many cities—Washington, Baltimore, Philadelphia, New York, Boston, Chicago, and others, and visited many of the dispensaries, hospitals and sanatoria still struggling in swaddling clothes, and gave them renewed impetus. In fact, the importance of the International Congress on Tuberculosis can scarcely be over-estimated, since the creation of state committees in advance of its meeting encouraged the formation later of local organizations, and Philadelphia came to be the center, to which the majority of States looked for models for their work.

Almost the only scientific medical man of eminence in Europe studying along lines interesting to workers in tuberculosis who failed to come was Metchnikoff. At the Pasteur Institute in Paris, where I had the pleasure of appealing to him, and the chagrin of appealing to him in vain, he answered: "Once I did go on a boat from Bordeaux around Spain to Marseilles. I became so seasick that nothing could persuade me ever to go on a boat again." I assured him that his was a coastwise trip where the sea was notoriously rough, unlike the broad bosom of the great Atlantic and that he was a passenger on a two for a penny steamer unlike the huge palatial liners conveying the millionaires of the world to the great port of New York, but he shook his massive old head and refused to be convinced.

On account of Dr. Flick's considerable accomplishment, the particulars of his life become interesting. He was born on August 10, 1856, five years before the beginning of the Civil War,

and died on July 7, 1938, just before reaching the age of eighty-two. He was introduced to life on his father's farm in a sparsely settled township of Cambria County, Pennsylvania, near the summit of the Allegheny Mountains, the dividing watershed between the Atlantic Ocean and the Mississippi Valley. His paternal ancestors came from the vicinity of Strassburg, which had been ceded by Germany to France more than a hundred years before their emigration,—his maternal ancestors from Bavaria. Hence in his own home he had the stimulation to learn both French and German and even before entering medicine could read them.

He was the ninth of twelve children, and two of the first eight are still living, one aged 94 and one 87. With this large family about him, and with money scarce as it was on farms, it was only very ardent desire for education which procured him the opportunity to attend St. Vincent's College, forty miles distant. His desire, however, proved greater than his physical strength, for at the age of seventeen, long before reaching his A.B., he broke down with his first attack of pulmonary tuberculosis. He had, however, sufficient of the classical college education prevailing in the early seventies, with Greek and Latin to aid in his mastery of English, to become an easy and fluent talker and writer.

On account of his own affliction even before he began his medical course at Jefferson at the age of twenty-one, his interest in the disease was aroused, and after a second, more serious, breakdown, following his internship in the Philadelphia General Hospital, he was easily lead into special study of it. This was less difficult for him on account of his knowledge of German and French, which allowed him to miss nothing of the work in Europe evolving at that time.

Conspicuously conscientious in his chosen profession, he was equally so as a citizen, and manifested publicly a similar interest in the cure and eradication of civic lawlessness. In fact at a time when opposition to the political powers was associated with even physical danger, he acted for years as a watcher at his polling place. Needless to say, such political views frequently

made his work harder in forwarding the campaign against tuberculosis, yet he not only refused to give them up, but refused to deviate from them.

Occasionally his medical confrères were inclined to think that some of his ideas for the furtherance of the tuberculosis campaign were presented over-boldly, but learning that he was equally forceful in stating his political views, and that the political powers were not anxious to break a lance with him, his medical confrères also extended to him special privileges.

Due to the fact that he was able to think clearly and act decisively, he had a natural flair toward the profession of law, and actually spent some time in the office of one of the most prominent legal firms in the city with the intention of fitting himself for medical jurisprudence. This was while waiting for patients after first opening his office, and was one of the causes of his second serious breakdown. It added, however, to his capability of clear thinking and a time came when there were but few whose instant reactions to a suggested proposition were more frequently correct. Learning from previous experience to depend on this judgment, when the time for action came, he showed no hesitation in going ahead.

For instance, in spite of the fact that, in the beginning of the campaign against the disease, the most widespread effort was spent on the treatment and cure of early cases, he made as much of a point of the care of advanced cases, especially in their removal from the home, to prevent them acting as a source of further contagion. And this good judgment has been confirmed, since it is now recognized that greater progress was made by emphasis on prevention than on cure, prevention showing its influence on the many in comparison with the small number benefited by cure.

In spite of his facility with the pen, so much of his time and energy were spent on organization and executive management that he was not so prolific a writer as many of his contemporaries, though his medical career extended over the fifty years during which medical magazines increased by the hundreds and medical articles by the thousands. Hence there are only about twenty

medical articles and six historical articles from his pen and three published books, the most noteworthy of the latter being that entitled "The Development of our Knowledge of Tuberculosis," published in 1925. The majority of the medical articles were written during his early years while endeavoring to inculcate in lay people and other physicians the doctrine of the communicability of tuberculosis. It was his proposal to make tuberculosis a disease registrable to the Board of Health which brought about the criticism of him by the College of Physicians in 1894, and allowed New York City the enviable distinction of becoming first in this field.

He had practically no light side to his character, no hobby in the way of games or sports, no inclination toward the theatre or movies, no desire for social visiting. An earnest student with a mind directed only to the higher things of life, even his casual reading was of the profound type and was devoted to history and classical authors like Goethe, Schiller and Cardinal Newman. Only under exceptional circumstances was a novel found in his hands. He was domestic to a high degree, earnestly believed that children were given to parents to be personally cared for by them, and his only periods of relaxation were in their company at home or at a summer resort. He had seven children and ten grandchildren, and, due to his devotion and care, all still survive.

Analogously, in his medical career he had the satisfaction of seeing survive him his various foundations, which had proven so instrumental in the reduction of the deathrate from tuberculosis from more than two hundred and fifty per hundred thousand population to sixty-six, and from first to sixth place in the causes of death.

Memoir of Michael A. Burns, M.D.*

By Edward A. Strecker, M.D.

Michael A. Burns died at Jefferson Hospital on March seventh, 1938, at the too early age of fifty-three. Dr. Burns had a distinguished neurological career. It began as a junior assistant to Dr. Francis Dercum at Jefferson Medical College in 1909 and ended with the important post of Professor of Neurology in the same school, his medical Alma Mater.

He gave freely of his neurological ability as a consultant to general and special hospitals including the Institute of the Pennsylvania Hospital.

He was a Fellow of the College of Physicians of Philadelphia and the American College of Physicians; a member of the American Psychiatric and the American Neurological Associations, and a former President of the Philadelphia Neurological Society.

In his extremely busy professional life he found time to lecture throughout the country and to contribute effectively to neurological literature.

Dr. Burns played a brilliant part in the neurology of the World War and was Consultant in Neuro-psychiatry to the District of Paris from December 1918 until June 1919.

Dr. Burns married Margaret Keenan of Philadelphia in 1910 and there are two sons, one in college and the other in the United States Naval Air Service.

The Fellows of the College, including many friends of Michael Burns, deplore his passing, not only from the standpoint of a professional capacity which the world could ill afford to lose, but, also, sadly, because of the loss of a fine, true and above all, a generous friend who literally gave his life for others.

* Read January 9, 1939.

College Notes

Elected to Fellowship:

Harvey Bartle, jr.,[2] Frieda Baumann,[2] Robert Kyun Hyun Charr,[2] Bernard I. Comroe,[1] Harrison F. Flippin,[2] Norman E. Freeman,[1] Leonard C. Hamblock,[1] Romeo A. Luongo,[1] Hans May,[2] Merle Middour Miller,[1] Joseph Scattergood, jr.[1]

Necrology:

Robert Norton Downs, jr. February 9, 1939.

Resolutions of a Public Character Passed by the Council:

1. *Whereas* those sections of the proposed new charter for the City of Philadelphia, dealing with the Departments of Health and Medical and Social Welfare, are drawn for the improvement of civic activities in Philadelphia relating to public health, and

Whereas these sections form part of a program definitely projected for improvement of the general welfare of the citizens of this city,

Therefore, be it resolved that the College of Physicians of Philadelphia, which is vitally concerned with the problem of public health in Philadelphia, gives its strong endorsement and support to those sections of the proposed new charter for the City of Philadelphia dealing with the Departments of Health and Medical and Social Welfare. *January 24, 1939.*

2. The College of Physicians of Philadelphia has noted with interest the movement sponsored by the Medical Library Association to initiate a comprehensive abstract journal covering clinical medicine and surgery and including their various specialties.

The College of Physicians recognizes the very great labor and expense involved in such an undertaking; but it also recognizes the probability of an important service which might be rendered, especially to those at a distance from the larger libraries of the Country.

The College of Physicians hopes that the Board of Trustees of the American Medical Association will carefully survey this project with a view to undertaking it, if the service rendered will justify the labor and expense involved. *March 28, 1939.*

Professional and Civic Activities of the Fellows:

Alfred Stengel and Ralph Pemberton were recipients, in January, of the State's Meritorious Service Medal at a ceremony held at Harrisburg.

[1] Elected January 9, 1939.
[2] Elected March 1, 1939.

O. H. Perry Pepper received a Sc.D. degree, *honoris causa*, from Lafayette College, in 1938, and succeeded William J. Kerr, of San Francisco, as president of the American College of Physicians, March, 1939.

Edward A. Strecker is scheduled to deliver the seventh series of Thomas W. Salmon Memorial Lectures at the New York Academy of Medicine, April 14, 21, and 28, and a résumé of the lectures at the Academy of Medicine in Toronto on May 5. The general title of the lectures is announced as *Beyond Clinical Frontiers*.

Esmond R. Long delivered an Alpha Omega Alpha Lecture at Western Reserve University, January 25, 1939.

Eugene M. Landis, scheduled to deliver an Alpha Omega Alpha Lecture at Harvard University on April 28, gave the Noble Wiley Jones Lectures for 1938 at the University of Oregon, and received the degree of M. S., *honoris causa*, from Yale University, in 1938.

Louis H. Clerf received an LL.D. degree, *honoris causa*, from Villa Nova College, June, 1938.

Luther C. Peter received an LL.D. degree, *honoris causa*, from Gettysburg College, 1938.

Edward Weiss is to deliver during the spring a series of lectures on Medical Information at the School of Economy, Bryn Mawr College.

George M. Coates was elected president of the American Academy of Ophthalmology and Otolaryngology, October, 1938.

George B. Wood was elected president of the American Laryngological Association for the year 1938–39, and is serving as chairman for the School of Medicine in the organization formed to arrange for the University of Pennsylvania's bicentennial celebration.

Bernard J. Alpers, appointed, in 1938, professor of neurology at Jefferson Medical College, has been elected vice-president of the Association for Research in Nervous and Mental Disease.

John A. Kolmer assumed a position as consultant to the U. S. Public Health Service, January, 1939.

Walter Hughson is now consultant otolaryngologist to the Bureau of Child Hygiene, Washington, D. C.

William G. Leaman has been appointed assistant professor of medicine in charge of the department of cardiology, Woman's Medical College.

Donald C. Smelzer has been elected a Trustee of the American Hospital Association.

Carroll R. Mullen has been appointed attending surgeon, Wills Hospital, and instructor in ophthalmology, Jefferson Medical College.

Warren S. Reese has succeeded Leighton F. Appleman, retired, as attending surgeon, Wills Hospital.

John F. Sinclair is now consulting epidemiologist to the Presbyterian Hospital.

Burton Chance has been elected president of the Pennsylvania Home Teaching Society and Free Circulating Library for the Blind.

Recent Publications by Fellows:

Comroe, B. I., Collins, L. H., jr., and Crane, M. P. Internal Medicine in Dental Practice. Phila., Lea & Febiger, 1938.

Cowan, Alfred. Refraction of the Eye. Phila., Lea & Febiger, 1938.

Davis, Warren B. and Hodges, L. M.* A Boy from Kentucky. Phila., Priv. pr., 1938.

Dorland, W. A. N. American Illustrated Medical Dictionary. 18 ed. Phila., Saunders, 1938.

——— American Pocket Medical Dictionary. 16 ed. Phila., Saunders, 1938.

Fox, Herbert. Chronic Arthritis in Wild Mammals. Trans. Am. Philos. Soc. N. S., Vol. 31, pt. II. 1939.

Goepp, R. Max. Medical State Board Questions and Answers. 7 ed. Phila., Saunders, 1938.

Ivy, Robert H., and Curtis, Lawrence. Fractures of the Jaw. 2 ed. Phila., Lea & Febiger, 1938.

Jackson, Chevalier. The Life of Chevalier Jackson. New York, Macmillan, 1938.

Kolmer, John A., and Boerner, F.* Approved Laboratory Technic. 2 ed. New York, Appleton-Century, 1938.

Moon, Virgil H. Shock and Related Capillary Phenomena. London & New York, Oxford univ. pr., 1938.

Musser, John H., *ed.* Internal Medicine. 3 ed. Phila., Lea & Febiger, 1938.

——— Thirty Years After. New Orleans, Priv. pr., 1938.

Norris, George W., and Landis, H. R. M. Diseases of the Chest and the Principles of Physical Diagnosis. 6 ed. Phila., Saunders, 1938.

Packard, Francis R. Some Account of the Pennsylvania Hospital of Philadelphia from 1751 to 1938. Phila., Priv. pr., 1938.

Pelouze, P. S. Gonorrhea in the Male and Female. 3 ed. Phila., Saunders, 1939.

Peter, Luther C. Principles and Practice of Perimetry. Phila., Lea & Febiger, 1938.

Reimann, Hobart A. The Pneumonias. Phila., Saunders, 1938.

Riesman, David. Medicine in Modern Society. Princeton, Princeton univ. pr., 1938.

Smith, Lawrence W., and Gault, E. S.* Essentials of Pathology. New York, Appleton-Century, 1938.

Snodgrass, L. E. Observations on "The Shoulder"; a "Book Review." Phila., Priv. pr., 1938.

Strecker, Edward A., and Chambers, F. T., jr.* Alcohol; One Man's Meat ——. New York, Macmillan, 1938.

Thorington, James.* Refraction of the Human Eye and Methods of Estimating the Refraction. 3 ed. Rev. and ed. by J. Monroe Thorington. Phila., Blakiston, 1939.

*Non-fellow.

Officers and Committees, 1939

President

George P. Muller

Vice-President

Edward B. Krumbhaar

Censors

Thomas R. Neilson
Francis R. Packard
John H. Gibbon
Alfred Stengel†

Secretary

J. Harold Austin

Treasurer

T. Grier Miller

Honorary Librarian

Albert P. Brubaker

Elective Councillors

To serve until January, 1940
Francis Heed Adler
William R. Nicholson

To serve until January, 1941
E. J. G. Beardsley
John B. Flick

To serve until 1942

Eugene P. Pendergrass
Truman G. Schnabel

Council

The foregoing officers and the chairmen of the nine standing committees.

STANDING COMMITTEES

Publication

Thomas Fitz-Hugh, jr., *Ch'n*
Russell S. Boles
Joseph Stokes, jr.

† Died April 10, 1939.

Library

David Riesman, *Ch'n*
Wm. Egbert Robertson
Edward A. Schumann
Philip F. Williams
Horatio C. Wood
The Honorary Librarian (*ex officio*)

Hall

George M. Laws, *Ch'n*
Harry L. Bockus
Joseph T. Beardwood, jr.
W. Edward Chamberlain
Hubley R. Owen

Mütter Museum and College Collections

J. Parsons Schaeffer, *Ch'n*
Baxter L. Crawford
Harry P. Schenck

Finance

Isaac Starr, *Ch'n*
A. Lovett Dewees
Frederick Fraley
The President and the Treasurer (*ex officio*)

Scientific Business

Edward L. Bortz, *Ch'n*
Charles Leonard Brown
Eugene M. Landis
The President and the Secretary (*ex officio*)

Public Health, Preventive Medicine and Public Relations

Hobart A. Reimann, *Ch'n*
Samuel Bradbury
A. Parker Hitchens
Maurice S. Jacobs
Esmond R. Long
The President (*ex officio*)

Entertainments

Charles W. Burr, *Ch'n*
Gilson C. Engel
Edward Rose
The President (*ex officio*)

PRIZE COMMITTEES AND TRUSTEES

Nathan Lewis Hatfield Prize and Lectureship

(Until February, 1940)

Ralph Pemberton, *Ch'n*
Charles C. Norris
Ralph M. Tyson

Alvarenga Prize

Balduin H. E. Lucké, *Ch'n*
Henry C. Bazett
Garfield G. Duncan
I. S. Ravdin
Lawrence W. Smith

Mary Scott Newbold Lectures

(Until January, 1939)

Robert G. Torrey, *Ch'n*
Harold W. Jones
Grayson P. McCouch
The President and the Chairman of the Committee on Scientific Business (*ex officio*)

Weir Mitchell Oration

(Until February, 1942)

Francis W. Sinkler, *Ch'n*
Henry P. Brown, jr.
David L. Farley
Francis C. Grant
Edward A. Strecker

Trustees of Nathan Lewis Hatfield Prize and Lectureship

William D. Stroud
John B. Carson
J. Montgomery Deaver

Trustee Under the Will of Thomas Skelton Harrison

(Until February, 1941)

Charles J. Hatfield

OFFICERS OF THE SECTIONS

General Medicine

Chairman, J. Alexander Clarke, jr.
Clerk, Thomas Fitz-Hugh, jr.
Executive Committee, Richard A. Kern, Harold W. Jones, Edward Rose

Medical History

Chairman, Burton Chance
Clerk, Louis B. Laplace
Executive Committee, David Riesman, Francis R. Packard, Robert L. Gilman

Ophthalmology

Chairman, A. G. Fewell
Clerk, Warren S. Reese
Executive Committee, H. Maxwell Langdon, J. Milton Griscom, Charles R. Heed

Otolaryngology

Chairman, Warren B. Davis
Clerk, William Hewson
Executive Committee, Benjamin D. Parish, Walter Roberts, Curtis C. Eves

PUBLIC HEALTH, PREVENTIVE AND INDUSTRIAL MEDICINE

Chairman, MAURICE S. JACOBS
Clerk, JOHN H. ARNETT
Executive Committee, RANDLE C. ROSENBERGER, JOSEPH STOKES, JR., ALEX. H. DAVISSON

Staff of the College

Librarian, Editor, and Superintendent

W. B. McDANIEL, 2D

Curator of the Mütter Museum

JOSEPH McFARLAND

Clerk, OLGA LANG
Assistant Clerk, HELEN M. NASH

Assistant Superintendent, ROBERT G. MUIR

The Diagnosis and Treatment of Anemia*

By W. B. Castle, M.D.

Professor of Medicine, Harvard Medical School; Associate Director, Thorndike Memorial Laboratory, Boston City Hospital

Anemia may be defined as a decrease in the concentration of the red blood cells, of hemoglobin or of both, in the circulating blood, due to a failure of the blood-forming organs to keep pace with blood loss or destruction. The same result will obviously follow whether the rate of blood loss or destruction is so greatly increased as to exceed the utmost capacities of the blood-forming organs or whether a decrease in the rate of blood production below the natural rate of blood destruction occurs. In many clinical instances of anemia both processes are to some extent involved.

Because of its availability for study, the peripheral blood is of particular interest to the clinician. It is perhaps worth while to emphasize the face that, because the red cells, the granular white cells and the platelets are all contributed by the bone marrow, determination of their number and characteristics in blood films is important in estimating the functional state of the bone marrow. It is especially fortunate that the reticulocyte represents an intermediate form between the adult red cell and its precursors in the bone marrow (1). The precentage of reticulocytes can be determined by supravital staining with brilliant cresyl blue, and afterwards the dried film can be counterstained in the usual manner.

In a general way the characteristics of the peripheral blood when the bone marrow is physiologically hyperactive differ sharply from those observable when it is physiologically hypo-

* Mary Scott Newbold Lecture XLII, The College of Physicians of Philadelphia, March 1, 1939.

active. The former condition is well exemplified by the blood picture of congenital hemolytic jaundice, which almost invariably shows an increased percentage of reticulocytes, moderate to considerable leukocytosis with a relative increase of the young polymorphonuclear elements and increase in the number of platelets. In contrast to this peripheral reflection of industry on the part of the bone marrow is the blood picture in anemias in which the bone marrow is physiologically hypoactive, as indicated by aplasia or at least by hypoplasia. Chronic benzol poisoning serves as a typical illustration. Here, as is well known, few reticulocytes, leukopenia and decreased platelets are found in the circulating blood. Differential white blood cell counts indicate a scarcity of the granulocyte series, and those that are present have the multilobate character of the nucleus of the fully adult cell.

Nevertheless, a peripheral blood picture suggesting hypofunction of the bone marrow does not necessarily mean a scarcity of germinal cells in the bone marrow. Even in the typical example of benzol anemia the degree of marrow cellularity may present considerable variations (2) (3). In pernicious anemia, though few reticulocytes, leukopenia and thrombopenia are characteristic, the marrow is unusually cellular and primitive. This discrepancy has been explained by the concept of maturation arrest put forward originally by Peabody (4) to account for the sudden increase in reticulocytes in the peripheral blood and the increased maturity of the bone marrow manifest as a result of treatment with liver extract. The principle so enunciated has since been extended to explain the apparent contradiction between increased cellularity of the bone marrow and signs suggestive of diminished blood production in certain so-called aplastic or refractory anemias. On the other hand, the increased output of bile pigment in pernicious anemia, as in the classic hemolytic anemias, is, in the opinion of Krumbhaar (5), Dock (6), Rhoads (7) (8) and Barker (9), incompatible with decreased blood production. Moreover, the primitive cellularity of the bone marrow of untreated pernicious anemia resembles that of certain extreme cases of hemolytic anemia in the clinic and in the experimental animal

(10). The absence of increased reticulocytes in the peripheral blood of pernicious anemia is explained by Rhoads and his associates on the supposition that these elements are destroyed before leaving the marrow. If, then, the increase of bile pigment output is to be explained on other than the basis of increased blood destruction, it is necessary to refer to the hypothesis of Whipple (11), which supposes that the excessive excretion of bile pigment is due to a failure of its proper utilization, as in the normal individual, for the formation of new erythrocytes. For the purposes of this lecture this problem will be regarded as unsettled, and pernicious anemia is included among other anemias of nutritional deficiency of the bone marrow.

Red Cell Characteristics

The distribution frequency of the red cell diameters can be determined by the somewhat laborious procedure of Price-Jones (12). The hematocrit offers a more convenient method by which to determine the mean corpuscular volume and mean corpuscular hemoglobin concentration (13) (14). The thickness of the erythrocyte can be calculated on the basis of the assumption that it is roughly a right cylinder of known volume and diameter whose height is equal to the cell thickness (15) (16). The mean fragility of erythrocytes in hypotonic salt solution is apparently a function of the difference between the volume of the erythrocyte in isotonic salt solution and the volume of a sphere with the same surface (17).

A centrifuge capable of a speed of 2500 R. P.M. is necessary for determination of the mean corpuscular volume and mean corpuscular hemoglobin concentration by the use of the hematocrit. The method, however, has the distinct advantage of yielding objective values instead of giving merely an impression from inspection of a blood film. The collection of the single necessary sample of venous blood is, moreover, quite possibly more convenient than is the accurate measurement of several small amounts of capillary blood under conditions at the bedside not always favoring precision. From an oxalated blood sample several determinations can subsequently be made, including red

blood cell count, white blood cell count, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, icterus index, sedimentation rate and fragility.

On the basis of the mean corpuscular volume and mean corpuscular hemoglobin concentration, anemias can be divided into various groups. Thus, the terms macrocytic, normocytic and microcytic refer to the mean corpuscular volume of the cells; normochromic and hypochromic refer to the mean corpuscular

TABLE 1

Calculation of mean corpuscular characteristics (Wintrobe)

				Macrocytic Normochromic	Normal Normocytic Normochromic	Microcytic Hypochromic
Mean corpuscular volume	$= \frac{\text{Volume percentage of R.B.C.}}{\text{R.B.C. (millions)}}$	$\times$ 10 =		95 – 160μ^3	80 – 94μ^3	50 – 80μ^3
Mean corpuscular hemoglobin concentration	$= \frac{\text{Hemoglobin in grams}}{\text{Volume percentage of R.B.C.}}$	$\times$ 100 =		32 – 35%	32 – 35%	21 – 30%
Mean corpuscular hemoglobin	$= \frac{\text{Hemoglobin in grams}}{\text{R.B.C. (millions)}}$	$\times$ 10 =		30 – 52 $\gamma\gamma$	27 – 30 $\gamma\gamma$	14 – 26 $\gamma\gamma$
Color index	$= \frac{\text{Hemoglobin percentage}}{\text{R.B.C. (millions)}}$	=		> 1	> 1 <	1 <

hemoglobin concentration. Illustrative values are shown in Table 1. The use of the term hyperchromic is doubtful, as the normal hemoglobin concentration, unlike the color index, is not exceeded in any anemia unless it be congenital hemolytic jaundice. A microcytic or hypochromic anemia, unless associated with chronic infection, is almost always due to iron deficiency and will respond to such therapy. On the other hand, although pernicious anemia is a macrocytic and normochromic anemia, there are other kinds of anemia with such erythrocyte characteristics

which, unfortunately, do not respond to therapy with liver or stomach preparations. Thus, the character of the erythrocytes alone has its limitations and does not necessarily lead to a diagnosis. It cannot be too strongly emphasized that blood dyscrasias demand investigation from the point of view of the history, the physical examination and general laboratory tests, quite as much as do other conditions in clinical medicine.

Diagnosis in General

Because of the possibility that a type of anemia readily susceptible of treatment may occur as a part of or as the entire cause of ill health, the recognition of the existence of anemia is of practical importance. Because of his dyspnea or angina the patient with anemia may appear to be suffering from heart disease; his polyuria, edema and inability to concentrate the urine may suggest a renal condition; his indigestion may seem to be the manifestation of organic gastrointestinal disease. If paresthesias and ataxia are prominent symptoms, multiple sclerosis or tabes may be wrongly suspected. On the other hand, because of the vagueness of his complaints the patient may appear to be merely neurotic. Minot (18), for example, recently found that, on the average, about a year and a half had elapsed following the onset of definite symptoms before the diagnosis in 100 consecutive cases of pernicious anemia was established.

In all anemias the hemoglobin concentration is reduced. It is thus, in order to exclude anemia, only necessary as a routine measure to make a hemoglobin determination. If found to be abnormal, complete examination of the blood will naturally follow. For a definite diagnosis, however, examination of the morphology by appropriate needle or surgical biopsy of the bone marrow, lymph nodes or spleen may be essential (19) (20). A gastric analysis to determine whether anacidity is present or not after the subcutaneous injection of 0.5 mg. of histamine is a valuable procedure in the nutritional group of anemias. An account of the patient's diet during the preceding months may be illuminating. It is possible for the patient, but inexcusable for the physician, to be unaware of occult blood in the stool. Be-

TABLE 2

Classification of anemias

A. Anemias mainly due to blood loss or increased blood destruction (bone marrow physiologically hyperactive)

I. Blood loss
  (a) Acute
II. Increased blood destruction
  (a) Extrinsic causes
    Infections: streptococcus, Welch bacillus, malaria, bartonella, etc.
    Chemicals: lead, nitro-compounds, etc.
  (b) Intrinsic causes
    Abnormal red blood cells
      Congenital hemolytic jaundice
      Paroxysmal nocturnal hemoglobinuria
      Sickle cell anemia
      Erythroblastic (Cooley's) anemia
    Hemolysis in plasma
      Transfusion reactions
      Paroxysmal hemoglobinuria due to cold
      Lederer's anemia

B. Anemias mainly due to decreased blood production (bone marrow physiologically hypoactive)

I. Nutritional deficiency of the blood-forming organs
  (a) Substances effective in addisonian pernicious anemia
    Pernicious (Addison-Biermer) anemia
    Macrocytic anemias of the tropics: sprue, pregnancy
    Pernicious (macrocytic) anemia of pregnancy
    Macrocytic anemia of pellagra
    Macrocytic anemias of pathological conditions of the gastrointestinal tract
  (b) Vitamin C
  (c) Iron and other substances concerned with hemoglobin production
    Hypochromic anemias of infancy and childhood
    Chlorosis
    "Idiopathic" hypochromic anemia
    Hypochromic anemia of pregnancy
    Hypochromic anemias of pathological conditions of the gastrointestinal tract
II. Endocrine deficiency
  (a) Thyroid
  (b) Pituitary
III. Toxic inhibition of the blood-forming organs
  (a) Poisons of external origin, for example:
    Benzol and other cyclic compounds
    Arsphenamine
    Gold compounds
  (b) Toxins of internal origin
    Chronic infections
    Chronic nitrogen retention

TABLE 2—*Concluded*

IV. Physical injury of the blood-forming organs
  (a) External irradiation: x-rays
  (b) Internal irradiation: radioactive substances
V. Mechanical interference with the blood-forming organs
  Acute leukemias
  Chronic leukemias
  Hodgkin's disease
  Myeloma and plasmoma
  Metastatic cancer of the bone marrow
  Primary xanthomatoses
  Osteosclerosis
VI. Idiopathic disturbances of the blood-forming organs
  Congenital anemias of infants
  "Aplastic" anemia
  Macrocytic anemia of liver disease
  "Splenic" anemia (Banti's syndrome)

cause chronic foci of infection, nitrogen retention and hypothyroidism may be responsible for the anemia or render the effect of treatment unsatisfactory in any type of anemia, as a routine procedure it is well to exclude these.

In some patients a critical test of the effect of therapy under careful observation may be the only means of determining the nature of the patient's condition (1). It is never wise before a diagnosis is reached to confuse the blood picture by indiscriminate therapy. Once transfusion or treatment with liver extract or iron has been applied the original condition may be difficult to identify. Even if the patient recovers rapidly the time will come when it may be necessary to consider what type of maintenance treatment is indicated. It is a matter of moment to most patients to know whether or not they need to spend perhaps $50 to $100 a year in order to maintain adequate treatment with liver extract. If the original response of the patient was due to iron and the patient was also given liver extract, an unnecessary expense has been incurred and may be continued unwisely.

Classification

When it is established that the patient has anemia, the first point in diagnosis is to decide whether, on the one hand, the anemia is due to acute blood loss or increased blood destruction

or, on the other hand, to some type of defective bone marrow function. The general characteristics of the blood films in these contrasting types of anemia have been described above. In this lecture time permits only a brief review, beginning with those anemias in which the functional capacity of the blood forming organs is normal. Table 2 presents a tentative classification.

A. ANEMIAS DUE TO BLOOD LOSS OR INCREASED BLOOD DESTRUCTION

1. *Acute Blood Loss*

The anemia of uncomplicated acute blood loss is a condition from which spontaneous recovery always occurs, unless the patient dies of shock due to the original loss of blood volume or unless repeated blood loss finally results in the development of a chronic hypochromic anemia. Even a few minutes after a large hemorrhage leukocytosis and marked increase of platelets occur. The red blood cell and hemoglobin concentrations, however, do not change until tissue fluid has entered the blood stream, and thus may not reach their lowest point until 48 to 72 hours later. Daily reticulocyte counts in patients (14) or in experimental animals (21) will reveal a progressive increase, reaching a maximum on the fifth to seventh day, and thereafter a decline over a somewhat longer period of time, associated with a decrease of white blood cells and platelets. The temporary macrocytosis at the time of the reticulocyte response (14) need not cause confusion with pernicious anemia if the latter response is noted. At this time the red blood cells and hemoglobin begin to increase together and usually within four to six weeks the red blood cell count has become normal. Transfusion is obviously the treatment of choice in the initial stage of exsanguination. It is of interest that occasionally in a concealed gastrointestinal hemorrhage this transitory increase of reticulocytes in the peripheral blood may provide the first evidence of blood loss. In the later stages the hemoglobin concentration may lag behind the red cell count (14) so that the color index becomes less than 1. At this time the mean corpuscular volume of the red cells and their hemoglobin

concentration are somewhat reduced and iron is of value in accelerating hemoglobin production.

II. *Increased Blood Destruction*

The outstanding characteristics of the blood in anemias due to increased blood destruction are the more or less constantly increased reticulocytes, leukocytes and platelets in the presence of elevated serum bilirubin or, in very severe processes, free hemoglobin in the plasma or even in the urine (22). In chronic hemolytic anemias, because of the extraordinary ability of the reticulo-endothelial system to conserve the products of broken down red cells, the bone marrow continues actively to make blood and the erythrocytes in circulation continue to be approximately normal in volume and hemoglobin concentration. The frequent enlargement of the spleen and liver, especially in chronic hemolytic anemias, is probably due to increase in cellularity necessary for dealing with the increased pigment metabolism.

The primary causes of hemolytic anemias may be arbitrarily divided into extrinsic and intrinsic ones. Among extrinsic factors are recognized infections of the circulating blood stream by various organisms, such as the streptococcus, the Welch bacillus, the malaria parasite or the bartonella bacilliformis of Oroya fever (23). It is of interest that frequently the anemia of subacute bacterial endocarditis has the essential characteristics of a hemolytic process. Exposure to chemicals, such as lead (24), trinitrotoluol (25), arsine (26), phenylhydrazine and sulfanilamide (27), also results in hemolytic anemia. The diagnosis of septicemia depends on the identification of the organism in the blood stream. With septicemia there are of course the usual constitutional signs in addition to a rapidly developing anemia. Severe hemolytic anemias due to chemicals or crises of blood destruction in other hemolytic anemias may, however, also be accompanied by fever, but the negative bacteriological evidence will usually distinguish these conditions. The mechanism of blood destruction in the anemias due to septicemia probably involves destruction of red cells by hemolytic toxins or by actual

invasion of the red cell by the organism. The mechanism of the action of the chemical agents is far from clear.

Treatment is primarily directed at the elimination of the infectious agent or the removal of the individual from exposure to the toxic chemical. In both instances repeated transfusions may be useful to prevent the blood values from reaching too low a level before recovery has begun.

Certain hemolytic anemias appear to be the result of intrinsic defects of the red blood cells. How in congenital hemolytic jaundice the increased fragility in hypotonic salt solution of the red blood cells is related to their increased destruction in the body is not understood. In paroxysmal nocturnal hemoglobinuria (22) (28) the red cell is peculiarly susceptible to hemolysis, both *in vivo* and *in vitro*, when the acidity of the plasma is increased within the physiological range (29) (30). Although the plasma constantly contains some free hemoglobin, the normal increase in the acidity of the plasma during sleep is apparently the factor in these patients which often causes the patient to pass dark urine containing hemoglobin on arising in the morning (29). In contrast to other types of hemolytic anemia the leukocytes are not increased and there is usually moderate thrombocytopenia. In sickle cell anemia, a condition confined, with few exceptions, to negroes, there is characteristic change in the form of the erythrocytes on anoxemic stagnation of the blood *in vivo* (31) or *in vitro* (32). The so-called erythroblastic anemia, the clinical features of which have been well described by Cooley (33) and others (34) (35), is also probably due to some type of defective red blood cell formation resulting in an increased rate of destruction with variable numbers of normoblasts and reticulocytes in the blood stream, together with leukocytosis and increased numbers of platelets. The affected children are almost always of southern Italian or Greek origin. The anemia is usually first noticed in early childhood and the majority of the patients die before puberty is attained. Physical examination discloses prominent eyes with epicanthal folds and exaggeration of the frontal and malar bosses, givin a Mongolian appearance. The skin has a muddy or olive color and the sclerae may show a

slight degree of icterus. The spleen and liver are usually enlarged. In all these conditions the erythrocytes display a normal or decreased fragility in hypotonic salt solution; and changes in the bones, presumably due to hyperplasia of the marrow, are often demonstrable by the x-ray (35). With the crises of blood destruction in any of these anemias, and this is especially common in sickle cell anemia, the concomitant fever and abdominal pains may suggest a surgical condition.

The intrinsic causes of hemolytic anemias in which the plasma is primarily at fault include the blood destruction following the transfusion of erythrocytes for which the recipient's plasma carries an isoagglutinin and isohemolysin (36). Paroxysmal hemoglobinuria following exposure to cold, which occurs usually in syphilitics, is due to a plasma hemolysin which becomes active after chilling of the blood. *In vitro* the hemolysin can be adsorbed in the cold by the patient's or by normal red blood cells and becomes active on warming to body temperature (37). Chill, fever and hemoglobinemia and later bilirubinemia are associated with the blood destruction in both these conditions. The acute hemolytic anemia (38) in children originally described by Lederer (39) is, according to Dameshek (40), caused by the development of a hemolysin active on cells of all blood groups *in vitro*. Because of its acute febrile course an infectious cause has been sought, but without success. In these anemias the fragility of the erythrocytes in hypotonic salt solution is usually normal.

It is well known that splenectomy is eminently successful in the treatment of congenital hemolytic jaundice. Although the fragility of the erythrocytes may be temporarily increased, this abnormal feature is restored to normal. Presumably by removal of the enlarged spleen, an organ importantly concerned with blood destruction and the conservation of hemoglobin precursors is eliminated. The decreased demand for erythrocytes results in the ability of the bone marrow to maintain relatively normal blood values. The temporary increase of resistance of the red cells following splenectomy is probably due to the resultant mild deficiency in hemoglobin production. After splenectomy the red blood cells transiently resemble the relatively flat erythrocytes

(41) of hypochromic anemia which are unusually resistant to hypotonic salt solution (16) (42). Moreover, in occasional cases of atypical hemolytic jaundice the erythrocyte fragility may be almost normal when the anemia is distinctly hypochromic (43). An account of such a patient was recently given me by Dr. O. H. Perry Pepper.

According to Curtis, Doan and Wiseman (44), splenectomy in congenital hemolytic jaundice is not contraindicated in a phase of rapid blood destruction because the removal of the spleen results in an immediate rise of the blood values, sometimes by as much as 20 per cent. Splenectomy in other types of hemolytic anemia is rarely of much value, though it is a logical procedure, especially if the organ is enlarged. No treatment other than transfusion is known for paroxysmal nocturnal hemoglobinuria. Splenectomy does not significantly diminish the anemia, though the nocturnal increase of hemoglobin in the urine may be abolished (29). Proper antisyphilitic treatment will usually cause cessation of the paroxysms of hemoglobinuria and anemia resulting on exposure to cold in patients with this particular type of hemolytic anemia. Although clinically cure is usually complete, *in vitro* studies may continue to show the presence of a hemolysin activated by exposure to cold (37). The patient with Lederer's anemia can usually be successfully carried over its course of a few weeks by means of transfusions.

There are described in the literature various instances of so-called acquired hemolytic jaundice. Chronic infections, such as malaria, syphilis and tuberculosis, are stated to result in such types of hemolytic anemia (45). In some of these patients careful investigation will, however, demonstrate a familial incidence of jaundice or of increased fragility of the erythrocytes. In this connection the terminal stage of the condition or group of conditions recently described by Hickling (46) as nonleukemic myelosis deserves mention. The chronic course, splenomegaly, presence of immature red and white cells in the peripheral blood, slight decrease in hypotonic resistance of the erythrocytes and mild jaundice may cause confusion either with aleukemic leukemia or with hemolytic jaundice. In these patients, however,

the platelets are often diminished in number and a history of purpura or of arthritis is frequently obtained. The exact nature of the disease is uncertain, but myeloid metaplasia may be a prominent feature and there may be appearances in x-ray pictures of the bones which are suggestive of osteosclerotic edema or of Paget's disease. It is therefore probably to be classed among the anemias due to mechanical interference with the bone marrow rather than with the hemolytic anemias. Irradiation of the patient, in contrast to its beneficial effect in leukemia, may diminish erythropoietic activity; and splenectomy may remove an organ probably making a valiant effort to complement the failing activity of the bone marrow.

B. ANEMIAS DUE TO DECREASED BLOOD PRODUCTION

In the anemias next to be discussed there is presumptive evidence of a failure on the part of the bone marrow to supply sufficient red blood cells to keep pace with the normal rate of removal. In certain instances, however, the gross extension and the increased cellularity of the marrow and the increased output of bile pigment give rise to the belief that to some extent an increased rate of blood destruction may be involved, as discussed earlier in this lecture. There is, however, comparative absence of those signs in the peripheral blood which are usually indicative of bone marrow activity.

1. *Nutritional Deficiency*

In this group of anemias it is assumed that erythrocyte or hemoglobin production is subnormal because of nutritional deficiency of three distinct types—respectively, "liver extract," vitamin C, and iron. Pernicious and related macrocytic anemias and the macrocytic anemia of vitamin C deficiency present a normal hemoglobin concentration. On the other hand, in hypochromic anemia microcytosis and decreased hemoglobin concentration are diagnostic features, and the outstanding difficulty seems to be with the production of hemoglobin.

(a) *Deficiency of "Liver Extract."* Pernicious and related macrocytic anemias have in common the characteristic of re-

sponding to the parenteral administration of relatively crude fractions of liver soluble in 70 per cent alcohol (47). This criterion applies to addisonian pernicious anemia (48), to the macrocytic anemia of pregnancy (49), to the macrocytic tropical anemia of India (50), to the macrocytic anemia of sprue (51) and pellagra (52), and to the macrocytic anemia of celiac disease (53) and fish tape-worm infestation (54). Moreover, in a variety of clinical conditions involving dietary disturbance and in such abnormalities of the intestinal tract as total gastrectomy, short circuits and stenoses of the bowel, macrocytic anemia responding to liver extract has been reported (55) (25). The blood picture common to these anemias is macrocytosis of variable degree, sometimes as great as is seen in any condition, moderate leukopenia with relative reduction of the granulocytes and some degree of thrombopenia. Hyperbilirubinemia, by no means a constant finding even in pernicious anemia, is very rarely seen in the tropical macrocytic anemia of India (56).

To a variable extent in each glossitis, achlorhydria and diarrhea are found. Achlorhydria is practically universal in addisonian pernicious anemia but rare, for example, in the tropical macrocytic anemia of India. Neural manifestations are commonest in pernicious anemia and in pellagra, in which last macrocytic anemia is least prominent. Sprue, celiac disease and pellagra are the conditions in which glossitis and gastrointestinal symptoms most regularly appear. Nevertheless, many patients present exceptions and unless viewed broadly nosological terms are confusing.

In any of the anemias of this group gastrointestinal or neural symptoms may be found in the presence of relatively little anemia or even with a blood picture of hypochromic anemia. Besides lack of iron there are commonly associated other forms of nutritional deficiency. This is clear, for example, with respect to the lingual and dermal manifestations of pellagra, upon which the striking therapeutic value of nicotinic acid has recently been shown (57). This substance is, however, apparently without effect upon the blood level of pernicious anemia (58) (59). The fact that certain macrocytic anemias, including pernicious anemia, respond to

autolyzed yeast preparations may mean either that residual gastric activity converts these substances into the active principle of liver extract (60) or that there is an actual direct deficiency of some other factor in the autolyzed yeast (58) 61). Even with relatively purified liver extracts the operation of multiple factors in the remisssion in pernicious anemia has been suggested (62). Moreover, Wills (56) has recently shown that the tropical macrocytic anemia of pregnancy fails to respond to certain purified liver extracts highly potent in addisonian pernicious anemia. It is necessary, therefore, to consider these various anemias as manifestations not of a single common deficiency but of various members of a group of principles present in relatively crude therapeutic preparations of mammalian liver.

For the elaboration of the crude therapeutic principle or principles active in pernicious anemia and found in the normal mammalian liver a thermostable constituent of the food, probably some as yet unidentified portion of the vitamin B complex (60), is acted upon by a thermolabile substance (63), probably an enzyme (64) (65), secreted in the stomach (60) and possibly in the duodenum (66) (67). It can be shown experimentally that deficiency of food, of gastric secretion or of intestinal absorption may, individually or in combination, operate to produce a final defect of an active principle in the liver (60). It has been suggested that disease of the liver itself may interrupt a sequence of internal metabolic processes essential for the formation, storage or release of this principle (68). Such patients only occasionally show a dramatic response to the administration of liver extract. This fact is, nevertheless, not necessarily inconsistent with the hypothesis of an interruption of an internal metabolic process.

When maximal doses of active principle are given orally or parenterally to patients with pernicious anemia reticulocytes appear in increased numbers in the peripheral blood within five days, reaching a peak usually on from the sixth to the tenth day after the beginning of treatment (1). The percentage of reticulocytes bears an inverse relationship to the initial level of the red blood cells. The red blood cell values progressively increase

at a rate again somewhat inversely proportional to the initial red blood cell level until at the end of about six weeks the red blood cell values are usually normal (69). At the end of this time the blood picture, including the leukocytes and platelets, shows very little departure from the normal. Lack of available iron in the diet in some instances results in a lag in the hemoglobin production, so that the characteristics of a moderate hypochromic anemia may be temporarily manifest and easily corrected by giving inorganic iron in various forms.

The responses of the macrocytic anemias of other members of this group than addisonian pernicious anemia, even to the parenteral administration of liver extract, are not usually as uniform and rapid as in pernicious anemia. For example, in sprue, response to usual amounts of parenterally administered liver extract is slow (51) or even absent (70). It is a not infrequent occurrence with any member of this group of macrocytic anemias, especially in those with prominent gastrointestinal symptoms, that the oral administration of liver extract is almost or quite ineffective (71). Under these circumstances the parenteral administration of usual doses may be apparently normal in its effect, suggesting that difficulty with the absorption from the alimentary canal is present (72) (73).

The value of relatively crude extracts of liver for parenteral administration has been demonstrated on the other common manifestations of this group of conditions. Thus with usual dosage the tongue and gastrointestinal symptoms in pernicious anemia are rapidly improved. Within a few days papillae reappear on the tongue (25) (51). Gastroscopic studies show likewise an abatement of the gastritis (74). In sprue the diarrhea may be resistant to anything but huge daily dosage of parenteral liver extract (70). After effective therapy x-ray studies of the small intestine show a return to normal (75), and the absorption of fat (76) and of glucose (73) is likewise enhanced. The neural manifestations of pernicious anemia in the absence of complications, especially decubitus or chronic urinary tract infection, can always be arrested by adequate dosage of parenteral liver extract (77). The degree of recovery of nerve function depends on the

duration and extent of the previous injury. Numerous papers describe the results of treatment in various special conditions with macrocytic anemia (25). Surgical intervention may result in a return to normal in individuals with short circuits of the intestine (78). With this exception, in any of these conditions treatment with sufficient active principle by the oral or parenteral route must usually be continued indefinitely. Because the lingual, gastrointestinal and neural manifestations may appear in patients with very little evidence of disturbance of blood formation or in association with other types of nutritional deficiency, it should be appreciated that a presumptive diagnosis of "liver extract deficiency" depends as much on the history and physical examination as on the actual blood examination (18).

Desiccated stomach (79) (80) is as efficient an oral remedy as is liver extract, but cannot be effectively administered in any form parenterally. The potentiating action of stomach tissue on a factor present in crude liver extracts is made use of in commercial combinations of desiccated stomach and liver extract (81) (82). These combinations are at present the most potent sources for oral administration. Because the active principle of liver extract is from thirty to sixty times more effective on parenteral administration than on oral administration (83), it is usually more economical and more certain to treat patients by the former method (84). Experience shows that it is difficult, especially after a return to health has occurred, to persuade all patients to continue to take material by mouth with regularity. Any patient with severe neural manifestations should probably be given the benefit of the parenteral method of treatment with its facility of introducing promptly large amounts of active principle.

It is of practical importance that the medical profession have knowledge of the effectiveness of various commercial preparations for the treatment of these anemias. Refinements and variations in different commercial methods of preparation of liver extract render uncertain the definitions of potency in terms of the amount of original liver. The recent revision of the United States Pharmacopoeia (85) has resulted in certification of the potency of liver and stomach preparations in terms of units evaluated by

clinical trial. A unit is that amount of the preparation which has been shown on daily administration in suitable patients to produce a satisfactory reticulocyte and red blood cell increase (86). It should be emphasized that this does not necessarily mean that a unit is the minimal amount capable of evoking such a response and that therefore U.S.P. units are not necessarily interchangeable from one product to another. Satisfactory commercial preparations for intramuscular use containing as many as 15 units per cubic centimeter are now available (87). Because it is not yet certain, however, that for controlling neural and gastrointestinal manifestations such concentrated preparations are as effective as those less refined, for the present no greater unitage will be assigned to preparations recognized by the Pharmacopoeia (88). As the preparation of parenteral extracts from existing oral liver fractions is a relatively simple matter, certain clinics and hospitals find it desirable to prepare their own extracts for intramuscular use. Such a conversion to a parenteral product has the economic recommendation that it results in sixty times as many units of material.

(b) *Deficiency of Vitamin C.* In certain cases of clinical scurvy the peripheral blood picture may be entirely indistinguishable from that of pernicious anemia and the bone marrow may show a suggestive megaloblastic quality (89). Such anemias, however, under carefully controlled conditions do not respond to liver extract administration, but do exhibit maturation of the cells of the bone marrow and characteristic reticulocyte responses in the peripheral blood on the administration of vitamin C (89) (90). The evidence thus seems convincing that a deficiency of this vitamin is mainly responsible for the anemia.

(c) *Deficiency of Iron.* It is gratifying to know that these hypochromic anemias are usually immediately recognizable from the characteristics of the peripheral blood. Although leukopenia and thrombopenia are rarely a striking and decidedly not a constant finding, the distinctly lowered color index, the reduction in mean corpuscular volume and especially in mean corpuscular hemoglobin concentration make confusion with any other type of anemia except that of chronic infection nearly impossible.

Loss of available iron, relative or absolute, is the dominant etiological defect. The commonest cause is chronic bleeding, whatever its origin, including menstruation. In childhood rapid growth associated with increase in the circulating blood volume may result in too little available hemoglobin to fill adequately the increasing total number of erythrocytes in a growing circulating blood volume (91). In pregnancy the demands of the infant for hemoglobin may deplete the maternal supply (92) (93). Surveys of the diet histories of patients with hypochromic anemia in various parts of the world usually indicate poor general nutrition (94) (95). Gastric anacidity and intestinal disorders are so common in more sporadic instances in the adult group that it must be inferred that difficulty with the absorption of food iron is an important conditioning cause (96). In such diseases as pellagra, sprue and even in pernicious anemia iron deficiency may occur and modify greatly the usual macrocytic anemia. In the adult male bleeding from the gastrointestinal tract is perhaps the commonest cause, other than obvious external hemorrhage, of hypochromic anemia. The blood picture and response to therapy with iron are not significantly different whatever the cause of the anemia. The fact that, for example, the nutritional anemia (91) of infants, chlorosis (97), idiopathic hypochromic anemia (98), Plummer-Vinson syndrome (99), the hypochromic anemia of pregnancy (93) and hookworm anemia (95) carry different names need not confuse us. In view of their common blood picture and satisfactory response to treatment with iron it is unnecessary to describe here the clinical particulars, which have been widely recorded in the medical literature.

It is obvious that, because hemoglobin is a combination of iron, porphyrin and globin, deficiencies other than iron may be involved in the etiology of hypochromic anemia. Whipple's classic observations indicated a number of foods useful in promoting hemoglobin formation in dogs. Later he and his associates (100) found that a fraction of liver precipitable by 70 per cent alcohol, and so differing from the alcohol-soluble fraction effective in pernicious anemia, was especially active in forming hemoglobin. Recently certain amino acids (101) and riboflavin

(102) have been found to be active under particular experimental conditions. Clinically, although the liver fraction has some hemoglobin producing power aside from its content of iron (95) (103), therapy with an equal weight of any iron salt is far more effective. Since copper is now known not to be deficient in the blood in hypochromic anemias (104) and since it is present as an impurity in most iron preparations it has no theoretical accessory value. Indeed, convincing evidence of its practical utility in the clinic is lacking.

In any of the types of severe hypochromic anemia mentioned above the daily oral administration of inorganic iron, whether in the form, for example, of ferrous sulphate (12 grains) or ferric ammonium citrate (90 grains) or as reduced iron (45 grains) (105), causes an increase in the reticulocytes, reaching a maximum usually from the fourth to the seventh day. Roughly equivalent daily doses of common preparations are ferrous sulphate, 12 grains, ferric ammonium citrate, 90 grains, reduced iron, 45 grains. The hemoglobin at first increases at the rate of about 1 per cent a day and then less rapidly as normal values are approached (106). The hemoglobin usually rises faster than the red blood cell count. The mean corpuscular volume and finally the mean corpuscular hemoglobin concentration return to normal, usually by the end of four to six weeks. Provided the original cause of blood loss is permanently eliminated, further treatment with iron is unnecessary (91). In adult females, however, before the menopause there is a regularly recurrent form of blood loss. In pregnancy iron should always be used as a prophylactic, quite as calcium is given and for similar reasons (107).

Intramuscular injections of iron are of little value because many of the commercial preparations contain only a very small amount of iron. In rare instances the oral administration of even the necessary small doses of ferrous iron may produce such intestinal irritation as to be intolerable to the patient. Even less frequently, large oral doses of iron salts do not appear to be effective. Under these circumstances a slow increase in hemoglobin values can be obtained by two daily intramuscular injections, for example, of a neutral solution of 100 milligrams of ferric ammonium citrate (108) or of ferrous gluconate (109).

II. *Endocrine Deficiency*

Removal of the thyroid gland in animals has been shown to result in macrocytic anemia and moderate hyperplasia of the bone marrow. In such animals thyroxin, if given, results in increased blood production (110). Most patients with myxedema have a deceptive degree of pallor, but a moderate degree of anemia occurs in about half of them and is especially likely to be present in patients with gastric anacidity (111). Hypochromic anemia also occurs in myxedema. The fact that the administration of liver extract or of iron in suitable types of anemia of myxedema may produce some elevation of the blood values before thyroid extract is given suggests that the anemia is, in part at least, due to nutritional disturbances. In the practical management of such patients the importance of elevating the metabolism outweighs that of the cure of the anemia, which can usually be eliminated by using iron or liver extract appropriately in addition to thyroid extract (112).

Experimentally it has been demonstrated that following removal of the pituitary gland anemia develops. Under these circumstances in animals anoxemia has been found no longer to be an effective stimulus for reticulocyte and red blood cell production (113). Administration of anterior pituitary growth hormone devoid of thyrotropic hormone has been followed by reticulocyte and red blood cell responses. A few patients with anemia in association with pituitary disease have been reported (114) (115). The results of therapy on the anemia are in most instances difficult to assay. As with myxedema, the complication of nutritional deficiency and gastric anacidity may well play a rôle in the causation of the anemia (116). Practically speaking, it is unlikely that hormonal deficiency will be a factor in the anemia of patients with normal basal metabolic rates.

III. *Toxic Inhibition*

The anemias of this group are considered to be due to interference with normal bone marrow function by certain toxic substances, either absorbed from outside the body or elaborated by perversions of its internal metabolism. Exposure to benzol (117)

and, in certain instances, to other cyclic compounds (3) (118) apparently produces a blood picture characterized by a normochromic and normocytic or slightly macrocytic anemia, leukopenia and thrombopenia. The injection of arsphenamine (118) and of gold compounds (119) may result in a similar blood picture and leukopenia or purpura, respectively, may be prominent individual or combined features of various cases. Severe chronic disturbance of renal function when associated with marked elevation of the non-protein nitrogen of the blood results in a somewhat similar anemia (120) (121), though usually leukocytes and platelets are only slightly depressed. In patients with chronic local infections a similar toxic inhibition may be hypothecated (25). Although commonly a microcytic and slightly hypochromic anemia is seen (122) (123), normochromic or mildly macrocytic anemia does occur. Leukocytosis rather than leukopenia usually but not always accompanies the infection.

Among the various poisons of external origin the effects of benzol have received the most careful clinical study. In the usual case, the outstanding manifestations are bleeding from the mucous membranes due to thrombopenia; liability to the development of necrotic lesions in the oral cavity because of leukopenia; and anemia, either entirely due to toxic depression of the bone marrow or partly as a result of blood loss (124). The treatment of such patients is successful in a fair percentage of cases if transfusions are given to control the bleeding and to carry the patient along until the bone marrow begins to form more erythrocytes. Unfortunately, there is considerable risk of the patient acquiring an infection because of the leukopenia.

The more chronic anemias of this group have been designated "chronic aplastic anemia," "achrestic anemia" (125) or, recently, "refractory anemia" (3) because although the blood picture resembles somewhat that of pernicious anemia no response to therapy with liver extract occurs. Thus patients have recently been reported (3) in whom a history was obtained of exposure to various coal tar derivatives, such as benzol, hair dyes, hydroquinone, naphthalene and creosote. The bone marrow varied from hypoplasia to even hyperplasia with dense infiltration with

uniformly immature cells. The hypercellularity of the bone marrow is to be explained either on the hypothesis of maturation arrest (4) (11) or as due to increased blood destruction (7) (8) (9). Recent animal experiments indicate that amidopyrine (126) and indol (127) can rapidly produce hemolytic anemia in the experimental animal when nutrition is defective. In any of these conditions the occasional extreme reduction of granulocytes in the peripheral blood may lead to an erroneous diagnosis of agranulocytic angina if the simultaneous presence of anemia and thrombopenia is not appreciated.

Rheumatic fever, chronic tuberculosis and osteomyelitis provide common examples of the so-called "secondary anemia" of chronic infection. Occasionally, seemingly unimportant infections of the sinuses or prostate may be responsible. Leukopenia is infrequent because the infection itself usually causes leukocytosis. In exceptional instances thrombopenia with purpura is observed. It is inferred that inhibition of the bone marrow is produced by toxic products elaborated by the organisms or by the tissues destroyed by them.

The inhibitory effect of infection on the bone marrow is best illustrated by the occasional instance in which, in the course of a response to liver therapy in pernicious anemia, an intercurrent infection results in prompt suppression of reticulocytes and of red cell production (1). The anemia of malaria, although mainly due to increased blood destruction, apparently involves also a component of bone marrow inhibition. Thus termination of the infection with quinine at once results in a further and temporary augmentation of the already elevated percentage of reticulocytes (95).

Chronic disturbances of renal function, like chronic infections, often result in anemia (120) (121). Significant lowering of the blood values is not common unless the non-protein nitrogen of the blood remains for some time above 100 milligrams per cent. The retention of nitrogen may be due to chronic nephritis, congenital cystic kidneys, surgical removal of one kidney or prostatic obstruction. It is of interest that the blood phenols are reported as elevated in this type of anemia (128).

In this entire group of anemias therapy with liver extract, vitamin C and iron is usually of little avail. The elimination of chronic infection or restoration of renal function by relief, for example, of prostatic obstruction, may be successful. The skilful and judicious use of transfusions to keep the patient alive until for one reason or another increased blood formation has been brought about is the chief therapeutic measure. It is possible that the common action of these conditions is to disturb the metabolism of aromatic compounds in such a way as to prevent the utilization by the bone marrow of essential nutritional elements.

IV. *Physical Injury*

The anemias of this group are rare and result from undue exposure to x-rays or radium (129). Experience in the treatment of polycythemia vera shows that unless large doses of x-ray are given it is difficult significantly to depress erythropoiesis (130). Thus the ordinary therapeutic dosage of x-rays has little effect on erythrocyte production and modern methods of protection render occupational exposure slight. Accordingly, when severe anemia develops in the course of the irradiation treatment of, for example, leukemia or Hodgkin's disease, it is usually the result of invasion of the bone marrow by the disease process and not of irradiation.

The absorption of radioactive material is, however, a most effective means of injuring the bone marrow because the exposure is thereafter continuous. Radium, like calcium, is absorbed by the skeleton and in that strategic position has a most effective and enduring opportunity for exerting its destructive action on the bone marrow cells. Radioactive material should therefore never be administered in a form in which it can become freely disseminated throughout the body. Its disastrous effects, as seen in radium poisoning occurring in industry, may not appear until years after the termination of the exposure (131). Necrosis of the jaw, progressive anemia and finally the development of osteogenic sarcoma appear to be outstanding clinical manifestations.

The anemia of radium poisoning is usually macrocytic with a normal hemoglobin concentration and so is said to resemble pernicious anemia (132). Likewise, at first the bone marrow shows changes resembling those seen in that anemia. Eventually a replacement fibrosis of the marrow occurs (131). In various patients the inhibitory effect on the leukocytes or on the platelets predominates, but in the end stage there appears to be a fairly consistent peripheral blood picture of aplastic anemia. Except for the passive effect of transfusion and the theoretical possibility of eliminating radium, like calcium, from the body by the production of acidosis in the early stages of the condition, no treatment is likely to be effective.

V. *Mechanical Interference*

Certain types of anemia may be tentatively explained by supposing that the marrow cavity becomes occupied to a greater or less extent by cells other than those concerned with erythrocyte production (25). The mechanism of the defective erythrocyte production in acute and chronic leukemias, in Hodgkin's disease and miliary tuberculosis, in carcinomatosis of the bone marrow and in certain types of xanthoma and osteosclerosis differs in an important way from the inhibitory processes occurring with nutritional and hormonal deficiency or with toxic inhibition of the bone marrow. In the latter a more or less diffuse effect is theoretically produced. In the former certain areas of the bone marrow may possess normal function, though the total ability of the organ to produce adequate numbers of erythrocytes may be defective. It must be said that this mechanical explanation does not meet with the approval of certain competent authorities (133), who point out that the peripheral and unaffected areas of the marrow do not take over the compensatory activity which might be expected on the basis of this theory.

Whether the mechanical explanation is correct or not, an *appearance* of furious hematopoietic activity in the face of progressive anemia without blood loss or satisfactory evidence of increased blood destruction is frequently seen in the peripheral

blood of metastatic carcinoma (133) (134) (135). Thus, repeated blood films will usually show a few immature leukocytes and an elevated percentage of reticulocytes, but a disproportionately large number of nucleated erythrocytes of the normoblast or even erythroblast type. The hyperactivity of marrow function as reflected in the peripheral blood is at least what would be expected were certain of the areas of the marrow relatively unaffected. Eventually, when the marrow becomes sufficiently involved, the appearance of the peripheral blood may become consistent with any type of aplastic anemia.

The commonest forms of cancer which metastasize to the bones are those which arise in the breast, prostate, adrenal and thyroid. The primary focus may be recognized or, on the other hand, the evidence of the widespread character of the disease may become apparent only through x-rays of the bones or in seeking the cause of the anemia. The clew to the diagnosis is often the finding of unusual numbers of nucleated erythrocytes and immature leukocytes in circulation (25) (133).

Whether leukemia presents primarily as leukemia or as anemia depends largely on whether the leukocyte count in the peripheral blood is high or low. In either type some anemia is present. In the aleukemic forms the immaturity of the leukocytes in circulation should be suggestive. Apparently any type of leukocyte may assume "malignant" characteristics and either remain as a single or multiple localized tumor (lymphoma), become invasive of the body tissue (lymphosarcoma) or appear in quantities in the circulating blood (lymphocytic leukemia) (136) (137). The tendency to remain localized, often for years, is particularly characteristic of multiple myeloma (plasma cell tumor), which only rarely becomes manifest as plasma cell leukemia in the peripheral blood in association with anemia (138). Likewise, the usual peripheral clinical manifestations of Hodgkin's disease may be minimal and the fact that the presenting anemia is due to severe affection of the bone marrow may become apparent only through its histological study after biopsy (3).

In the diseases associated with the names of Gaucher, Niemann-Pick and Schüller-Christian (139) (140) (141) the production of

red cells in the bone marrow is probably interfered with by the presence of masses of reticulo-endothelial cells containing the abnormal metabolic substances characteristic of these diseases or by the fibrosis subsequent to this process (140) (141). Accounts of the blood pictures are far from complete because of the greater interest in the metabolic disturbance. Splenic puncture or bone marrow biopsy is sometimes necessary in distinguishing Gaucher's disease in children from erythroblastic (Cooley's) anemia.

Several types of pathological processes in the bone marrow apparently end in a fibrotic stage, among which may be mentioned the action of radioactive substances, disorders of lipoid metabolism, Hodgkin's disease and the condition described as osteosclerosis. The rare congenital condition known as marble bone disease is sometimes associated with anemia (23). It is usually recognized before puberty because of the multiple fractures and is not to be confused with the osteosclerotic anemia (142) or myelosclerosis (133) (143) of the adult. The latter is apparently a terminal stage in some instances of what is described as nonleukemic myelosis (46). Like other anemias of this group, nonleukemic myelosis or osteosclerotic anemia results in a normocytic or slightly macrocytic anemia with a variable number of somewhat immature white cells in circulation. The degree of immaturity of the leukocytes is usually not definitely consistent with leukemia. In some patients thrombopenia may be present and result in purpura at various stages of the disease, which is a process measured in years (46). Terminally there may be a peripheral blood picture suggesting some type of hemolytic anemia, especially because of a slight increase in the hypotonic fragility of the erythrocytes.

It is perhaps in this group of anemias that bone marrow biopsy is most useful as a diagnostic measure, both in distinguishing between the various members of this group of conditions and in differentiating them from anemia due to toxic inhibition of the bone marrow. X-ray examination of the bones is likewise an important aid but it should be borne in mind that, especially in children, rarefaction of the bones may occur whenever there is

distinct marrow hyperplasia. Even in adults, x-ray examination is not necessarily able to distinguish, for example, between metastatic cancer and multiple myeloma or even between certain cases of Hodgkin's disease and leukemia. The x-ray pictures of marble bone disease and of osteosclerosis both show evidence of increased density of the bone when control exposures of normal individuals are made. Spontaneous fractures are rare in osteosclerotic anemia, leukemia and Hodgkin's disease but common in marble bone disease, multiple myeloma and metastatic carcinoma.

The treatment of the anemia in these conditions is unsatisfactory except in the sense of temporary amelioration. Such success depends primarily on the degree of sensitivity to irradiation of the cell invading the marrow. Following irradiation in chronic leukemias not only a lowering of the white count is obtained, but frequently an elevation of the erythrocyte and hemoglobin values, sometimes associated with a reticulocyte response (144). The anemia of metastatic carcinoma of the bone marrow is rarely improved by irradiation though, in common with Hodgkin's disease and myeloma in which the anemia may be benefited by x-rays, relief of local symptoms may result. X-ray therapy of the sclerosing conditions of the bone marrow is naturally contraindicated. Among the xanthomatoses, the local bony defects of Schüller-Christian's disease may be obliterated by irradiation (145), but little is known concerning the effect of x-ray on the anemia in the lipoid diseases. In myelogenous leukemia Fowler's solution may produce a fall in white count and elevation of the erythrocyte level (146). Transfusion as a means of prolonging life is of use in all, but offers only a temporary and passive benefit.

VI. *Idiopathic*

Space does not permit a discussion of the congenital anemias of infants, including the various types of erythroblastosis fetalis.

The so-called splenic anemia, for which Banti laid down certain criteria, is usually associated with either cirrhosis of the liver, thrombophlebitis or other cause for increased pressure in the

splenic vein (147). The histology of the spleen is consistent with chronic passive congestion. Descriptions of the anemia of Banti's disease coincide precisely with those of modern hypochromic anemia, and the tendency to hemorrhages in the condition is probably responsible for the anemia in many instances. Occasionally macrocytic anemia is observed in patients who can be considered as fulfilling Banti's criteria (148). The value of splenectomy is doubtful except as a means of diminishing the liability to hemorrhage from esophageal varices (149) (150). The anemia of certain of the patients can be abolished by the administration of iron (151), but there is probably a toxic element similar to that found in cirrhosis of the liver which is in part responsible for the anemia. The diagnosis of splenic anemia is seldom made by postmortem examination, which usually discloses that some type of liver pathology was present as a cause for splenomegaly (152). The term splenic anemia is so inadequately descriptive that it had best be abolished.

The original description of Ehrlich of an idiopathic aplastic anemia as an unexplained, rapidly fatal process, usually of young adults, with a blood picture of leukopenia and thrombopenia by no means includes all of the cases that may be so classified. There are apparently more chronic forms, sometimes of months' or years' duration, in some of which, as described under the section on "Toxic Inhibition," a history of exposure to cyclic compounds has been elicited (2) (3), but in others of which even this clew is absent. It is now recognized that neither in the acute nor in the more chronic instances of such types of anemia is the bone marrow necessarily aplastic in a morphological sense, as it may be normal or even hyperplastic in appearance (2) (3). Nevertheless, in some of these patients with hyperplastic bone marrow increased blood destruction must be considered because of the increased output of bile pigment in the feces (9). No form of therapy other than transfusion has been found to be of benefit.

In conclusion, it must be stated that with regard to many of the anemias described in this lecture the etiology is either doubt-

ful or otherwise defined by competent authorities. In a sense, only with regard to the anemias of acute and chronic blood loss is the immediate causative mechanism entirely clear. We cannot explain satisfactorily the factors immediately responsible in most of the anemias due to increased blood destruction. Even in the anemias of nutritional deficiency the nature of the underlying processes can still be presented only in a schematic fashion. The active principle or principles of liver and stomach remain unidentified. Moreover, especially due to the excellent studies of Rhoads and his associates, the conception of maturation arrest in pernicious anemia is open to question and the possibility of a hemolytic process is raised in this and other anemias classified above as due to defective blood production.

In order to clarify the whole situation it would seem desirable that a complete understanding of the mechanism of hypochromic anemia should be worked out as probably the illustration of anemia most assuredly due to deficient blood production. Moreover, until such fundamental information as the mechanism of destruction of the normal erythrocyte has been obtained the etiology of the majority of the hemolytic anemias is likely to remain obscure. Thus, despite the great advances of the past few years, there remain ample opportunities for contributions by practitioners or by laboratory workers interested in the study of anemias.

BIBLIOGRAPHY

(1) Minot, G. R., and Castle, W. B.: Lancet, 1935, **2**, 319. (2) Thompson, W. P. *et al.*: Am. J. Med. Sc., 1934, **187**, 77. (3) Rhoads, C. P., and Barker, W. H.: J. A. M. A., 1938, **110**, 794. (4) Peabody, F. W.: Am. J. Path., 1927, **3**, 179. (5) Krumbhaar, E. B.: Am. J. Med. Sc., 1928, **175**, 523. (6) Dock, W.: Am. J. Clin. Path., 1938, **8**, 620. (7) Rhoads, C. P., and Miller, D. K.: Compt. rend. IIIme. Conférence internat. de path. géographique, Stockholm, 1937, p. 170. (8) Rhoads, C. P.: Cold Spring Harbor Symposium on Quantitative Biology, 1937, **5**, 410, Darwin Press, New Bedford. (9) Barker, W. H.: Arch. Int. Med., 1938, **62**, 222. (10) Steele, B. F.: J. Exper. Med., 1933, **57**, 881. (11) Whipple, G. H.: Arch. Int. Med., 1922, **29**, 711; Am. J. Med. Sc., 1928, **175**, 721. (12) Price-Jones, C.: Red Cell Diameters, Oxford Univ. Press, London, 1933. (13) Wintrobe, M. M.: J. Lab. & Clin. Med., 1931–32, **17**, 899. (14) Heath, C. W.: New England J. Med.,

1933, **209**, 173. (15) von Boros, J.: Ergebn. d. inn. Med. u. Kinderh., 1932, **42**, 635. (16) Haden, R. L.: Am. J. Med. Sc., 1934, **188**, 441. (17) Castle, W. B., and Daland, G. A.: Arch. Int. Med., 1937, **60**, 949. (18) Minot, G. R.: Med. Clin. N. Amer., 1934–35, **18**, 935. (19) Custer, R. P.: Am. J. Med. Sc., 1933, **185**, 617. (20) Dameshek, W.: Am. J. Med. Sc., 1935, **190**, 617. (21) Gordon, A. S.: Proc. Soc. Exper. Biol. & Med., 1933–34, **31**, 563. (22) Witts, L. J.: Lancet, 1936, **2**, 115. (23) Vaughan, J. M.: The Anaemias, 2nd Ed., Oxford Univ. Press, Humphrey Milford, London, 1936. (24) Aub, J. C., *et al.*: Medicine, 1925, **4**, 1. (25) Castle, W. B., and Minot, G. R.: Pathological Physiology and Clinical Description of the Anemias, Oxford Medicine, vol. 2, p. 589, Oxford Univ. Press, New York. (26) Bomford, R. R., and Hunter, D.: Lancet, 1932, **2**, 1446. (27) Harvey, A. M., and Janeway, C. A.: J. A. M. A., 1937, **109**, 12. (28) Hamburger, L. P., and Bernstein, A.: Am. J. Med. Sc., 1936, **192**, 301. (29) Ham, T. H.: New England J. Med., 1937, **217**, 915. (30) Dacie, J. V., *et al.*: Lancet, 1938, **1**, 479. (31) Scriver, J. B., and Waugh, T. R.: Canad. Med. Assn. J., 1930, **23**, 375. (32) Hahn, E. V., and Gillespie, E. B.: Arch. Int. Med., 1927, **39**, 233. (33) Cooley, T. B.: Am. J. Dis. Child., 1928, **36**, 1257. (34) Baty, J. M., *et al.*: Am. J. Dis. Child., 1932, **43**, 667. (35) Mandeville, F. B.: Radiology, 1930, **15**, 72. (36) Wiener, A. S.: Blood Groups and Blood Transfusion, Charles C. Thomas, Baltimore, 1935. (37) Mackenzie, G. M.: Medicine, 1929, **8**, 159. (38) O'Donoghue, R. J. L., and Witts, L. J.: Guy's Hosp. Rep., 1932, **82**, 440. (39) Lederer, M.: Am. J. Med. Sc., 1925, **170**, 500. (40) Dameshek, W., and Schwartz, S. O.: New England J. Med., 1938, **218**, 75. (41) Gordon, A. S., *et al.*: Am. J. Physiol., 1937, **120**, 150. (42) Daland, G. A., and Worthley, K.: J. Lab. & Clin. Med., 1934–35, **20**, 1122. (43) Gänsslen, M., *et al.*: Deutsches Arch. f. klin. Med., 1925, **146**, 1. (44) Curtis, G. M., *et al.*: Ann. Surg., 1936, **104**, 892. (45) Krumbhaar, E. B.: Am. J. Med. Sc., 1915, **150**, 227. (46) Hickling, R. A.: Quart. J. Med., 1937, **6**, 253. (47) Cohn, E. J., *et al.*: J. Biol. Chem., 1928, **77**, 325. (48) Minot, G. R., *et al.*: Am. J. Med. Sc., 1928, **175**, 581. (49) Strauss, M. B., and Castle, W. B.: Am. J. Med. Sc., 1933, **185**, 539. (50) Wills, L.: Brit. Med. J., 1931, **1**, 1059. (51) Castle, W. B., *et al.*: Arch. Int. Med., 1935, **56**, 627. (52) Ramsdell, R. L., and Magness, W. H.: Am. J. Med. Sc., 1933, **185**, 568. (53) Vaughan, J. M., and Hunter, D.: Lancet, 1932, **1**, 829. (54) Isaacs, R., *et al.*: Arch. Int. Med., 1928, **42**, 313. (55) Little, W. D., *et al.*: J. A. M. A., 1929, **93**, 1290. (56) Wills, L., and Evans, B. D. F.: Lancet, 1938, **2**, 416. (57) Spies, T. D., *et al.*: J. A. M. A., 1938, **110**, 622. (58) Ungley, C. C.: Lancet, 1938, **1**, 925. (59) Hansen-Pruss, O. C.: New England J. Med., 1938, **218**, 1050. (60) Castle, W. B.: Science, 1935, **82**, 159. (61) Wills, L., *et al.*: Biochem. J., 1937, **31**, 2136. (62) Jacobson, B. M., and Subbarow, Y.: J. Clin. Investigation, 1937, **16**, 573. (63) Castle, W. B., and Ham, T. H.: J. A. M. A., 1936, **107**, 1456. (64) Taylor, F. H. L., *et al.*: J. Clin. Investigation, 1938, **17**, 335. (65) Lasch, F.: Klin. Wchnschr., 1937, **16**, 810.

66) Meulengracht, E.: Acta med. Scandinav., 1935, **85**, 79. (67) Magnus, H. A., and Ungley, C. C.: Lancet, 1938, **1**, 420. (68) Wintrobe, M. M.: Arch. Int. Med., 1936, **57**, 289. (69) Isaacs, R., *et al.*: J. A. M. A., 1938, **111**, 2291. (70) Rhoads, C. P., and Miller, D. K.: J. A. M. A., 1934, **103**, 387. (71) Castle, W. B., *et al.*: Am. J. Med. Sc., 1931, **182**, 741. (72) Strauss, M. B.: J. A. M. A., 1934, **103**, 1. (73) Groen, J.: New England J. Med., 1938, **218**, 247. (74) Jones, C. M., *et al.*: Am. J. Med. Sc., 1935, **190**, 596. (75) Miller, D. K., and Rhoads, C. P.: Am. J. Med. Sc., 1936, **191**, 453. (76) Barker, W. H., and Rhoads, C. P.: Am. J. Med. Sc., 1937, **194**, 804. (77) Strauss, M. B., *et al.*: J. A. M. A., 1935, **104**, 1587. (78) Richardson, W.: New England J. Med., 1938, **218**, 374. (79) Sturgis, C. C., and Isaacs, R.: J. A. M. A., 1929, **93**, 747. (80) Bethell, F. H., and Goldhamer, S. M.: Am. J. Med. Sc., 1933, **186**, 480. (81) Reimann, F.: Med. Klin., 1931, **27**, 880. (82) Walden, G. B., and Clowes, G. H. A.: J. Biol. Chem., 1932, **97**, xi. (83) Castle, W. B., and Taylor, F. H. L.: J. A. M. A., 1931, **96**, 1198. (84) Murphy, W. P.: J. A. M. A., 1932, **98**, 1051. (85) Pharmacopoeia of the United States, Eleventh Decennial Revision, 1936. (86) Report on the Potency of Liver Products, J. A. M. A., 1938, **110**, 812. (87) Report on Liver Products by the United States Pharmacopoeia Anti-Anemia Preparations Advisory Board, New England J. Med., 1938, **218**, 620. (88) Second Announcement of the U.S.P. Anti-Anemia Preparations Advisory Board, J. Am. Pharm. Assn., 1938, **27**, 629. (89) Mettier, S. R., *et al.*: J. A. M. A., 1930, **95**, 1089. (90) Vaughan, J. M.: Tr. Roy. Soc. Trop. Med. & Hyg., 1934, **27**, 533. (91) Heath, C. W., and Patek, A. J., Jr.: Medicine, 1937, **16**, 267. (92) Strauss, M. B.: J. Clin. Investigation, 1933, **12**, 345. (93) Strauss, M. B., and Castle, W. B.: Am. J. Med. Sc., 1932, **184**, 663. (94) Davidson, L. S. P., and Fullerton, H. W.: Edinburgh Med. J., 1938, **45**, 1. (95) Rhoads, C. P., *et al.*: Medicine, 1934, **13**, 317. (96) Mettier, S. R., and Minot, G. R.: Am. J. Med. Sc., 1931, **181**, 25. (97) Patek, A. J., Jr., and Heath, C. W.: J. A. M. A., 1936, **106**, 1463. (98) Wintrobe, M. M., and Beebe, R. T.: Medicine,1933, **12**, 187. (99) Suzman, M. M.: Arch. Int. Med., 1933, **51**, 1. (100) Whipple, G. H., *et al.*: Am. J. Med. Sc., 1930, **179**, 628. (101) Whipple, G. H., and Robscheit-Robbins, F. S.: Proc. Soc. Exper. Biol. & Med., 1937, **36**, 629. (102) György, P., *et al.*: Am. J. Physiol., 1938, **122**, 154. (103) Barker, W. H., and Miller, D. K.: Am. J. Med. Sc., 1938, **195**, 287. (104) Sachs, A., *et al.*: Arch. Int. Med., 1935, **55**, 227. (105) Witts, L. J.: Proc. Roy. Soc. Med., 1931, **24**, 543. (106) Heath, C. W.: Arch. Int. Med., 1933, **51**, 459. (107) Corrigan, J. C., and Strauss, M. B.: J. A. M. A., 1936, **106**, 1088. (108) Heath, C. W., *et al.*: J. Clin. Investigation, 1932, **11**, 1293. (109) Reznikoff, P., and Goebel, W. F.: J. Clin. Investigation, 1937, **16**, 547. (110) Kunde, M. M., *et al.*: Am. J. Physiol., 1931–32, **99**, 469. (111) Lerman, J., and Means, J. H.: J. Clin. Investigation, 1932, **11**, 167. (112) Lerman, J., and Means, J. H.: Endocrinology, 1932, **16**, 533. (113) Meyer, O. O., *et al.*: Folia haemat., 1937, **57**, 99. (114)

Stodtmeister, R.: Deutsche med. Wchnschr., 1936, **62**, 2010. (115) Lawrence, J. S., and Van Wagenen, W. P.: Tr. Assn. Am. Phys., 1938, **53**, 152. (116) Snapper, I., *et al.*: Quart. J. Med., 1937, **6**, 195. (117) Hamilton, A.: Arch. Path., 1931, **11**, 434, 601. (118) McCarthy, F. P., and Wilson, R., Jr.: J. A. M. A., 1932, **99**, 1557. (119) Dameshek, W.: New England J. Med., 1934, **210**, 687. (120) Parsons, L., and Ekola-Strolberg, M.: Am. J. Med. Sc., 1933, **185**, 181. (121) Brown, G. E., and Roth, G. M.: Arch. Int. Med., 1922, **30**, 817. (122) Douglas, A. H., and Tannenbaum, H.: Arch. Int. Med., 1930, **45**, 248. (123) Kugelmass, I. N., and Lampe, M.: Am. J. Dis. Child., 1932, **43**, 291. (124) Hunter, F. T., and Hanflig, S. S.: Boston Med. & Surg. J., 1927, **197**, 292. (125) Israëls, M. C. G., and Wilkinson, J. F.: Quart. J. Med., 1936, **5**, 69. (126) Miller, D. K., and Rhoads, C. P.: J. Exper. Med., 1937, **66**, 367. (127) Rhoads, C. P., and Miller, D. K.: J. Exper. Med., 1938, **67**, 273. (128) Becher, E., and Litzner, S.: Klin. Wchnschr., 1926, **5**, 147. (129) Rolleston, H.: Quart. J. Med., 1930–31, **24**, 101. (130) Sgalitzer, M.: Wien. klin. Wchnschr., 1935, **48**, 675. (131) Martland, H. S.: Am. J. Cancer, 1931, **15**, 2435. (132) Martland, H. S.: J. A. M. A., 1929, **92**, 466. (133) Vaughan, J. M.: J. Path. & Bact., 1936, **42**, 541. (134) Waugh, T. R.: Am. J. Med. Sc., 1936, **191**, 160. (135) Jaffé, R. H.: Folia haemat., 1933, **49**, 51. (136) Krumbhaar, E. B.: J. A. M. A., 1936, **106**, 286. (137) Furth, J., *et al.*: J. A. M. A., 1935, **105**, 1824. (138) Muller, G. L., and McNaughton, E.: Folia haemat., 1931–32, **46**, 17. (139) Pick, L.: Am. J. Med. Sc., 1933, **185**, 453, 601. (140) Brill, N. E., and Mandlebaum, F. S.: Am. J. Med. Sc., 1913, **146**, 863. (141) Rowland, R. S.: Anomalies of Lipid Metabolism, Oxford Medicine, vol. 4, p. 214, Oxford Univ. Press, New York. (142) Chapman, E. M.: Am. J. Med. Sc., 1933, **185**, 171. (143) Anagnostu, J. L.: Folia haemat., 1933, **50**, 70. (144) Isaacs, R.: Am. J. Med. Sc., 1926, **171**, 20. (145) Sosman, M. C.: J. A. M. A., 1932, **98**, 110. (146) Forkner, C. E.: Med. Clin. N. Amer., 1931–32, **15**, 1057. (147) Thompson, W. P., *et al.*: J. Clin. Investigation, 1937, **16**, 571. (148) Wright, D. O.: Ann. Int. Med., 1934–35, **8**, 814. (149) Hanrahan, E. M., Jr.: Arch. Surg., 1925, **10**, 639. (150) Pemberton, J. de J.: Coll. Papers, Mayo Clinic, 1931, **23**, 639. (151) Davidson, L. S. P.: Lancet, 1934, **2**, 539. (152) Larrabee, R. C.: Am. J. Med. Sc., 1934, **188**, 745.

A New Approach to the Etiology and Treatment of Angina Pectoris*†

By William J. Kerr, M.D.

During the past four years we have observed that certain patients suffering from angina pectoris (as well as other cardiovascular complaints) were relieved by supporting the abdomen with a specially constructed belt. The classic type of patient presented a picture of obesity, with a protuberant, pendulous abdomen, exaggerated spinal curves, florid complexion, and poor posture. Dr. John B. Lagen and I have described previously other interesting findings in these cases. We have assumed that these patients were relieved of their pain by the belt because of alterations produced in the circulatory dynamics through support of the pendulous abdomen, the net result being that filling of the heart was improved. Dr. Espey F. Cannon[1] and I are now investigating the immediate changes in the circulatory dynamics brought about by application of an abdominal support in any given case of angina pectoris.

When in a reclining position at rest, the circulatory dynamics of a patient with postural defects, obesity and myocardial insufficiency are, for all practical purposes, essentially comparable to those of normal individuals in the same position. It is only when the abnormal subjects assume an upright posture and begin to exercise, that their functional incapacities become apparent. There are three chief factors compensating for changes in the circulatory system that are induced by the force of gravity with changes in posture. They are: (1) maintenance of tone by the splanchnic area, which prevents accumulation of blood in regions

* From the Department of Medicine, University of California Medical School, San Francisco.

Aided in part by a grant from the Christine Breon Fund for Medical Research.

† Mary Scott Newbold Lecture XLIV, The College of Physicians of Philadelphia, May 3, 1939.

[1] Lillie Spreckels Wegeforth Fellow in Internal Medicine.

where it would tend to accumulate by force of gravity; (2) changes in cardiac action as manifested by the changes in pulse-rate and blood-pressure; and (3) respiratory action, which helps raise the column of blood against the force of gravity. In the normal subjects, a combination of these three factors prevents any decrease in cardiac output when a change is made from recumbent to erect posture. In debilitated people, in whom splanchnic tone is diminished, in ptotic individuals, and in people who have obese and pendulous abdomens, one might readily expect a decrease in cardiac output and circulatory embarrassment when an upright posture is assumed. This is well illustrated by ordinary syncope as seen in orthostatic hypotension, and in attacks induced by standing still for a long time. The cause of this phenomenon is inadequate cerebral circulation brought about by a loss of splanchnic tone. It is our belief that this lack of compensation for postural changes is primarily responsible for lowering the efficiency of the already impaired coronary circulation in our patients with angina pectoris and postural defects.

In any case of true angina pectoris, we are dealing with an individual whose symptoms arise as a direct result of the inadequacy of his coronary circulation during times of increased demand upon the myocardium. All of our common therapeutic measures in angina pectoris are directed toward one end—namely, that of improving the efficiency of the coronary circulation. We believe we have been able to accomplish this end by a measure more rational and effective than any that have been suggested to date, and one which does not require drugs, injection of autonomic nerves or any surgical procedure.

It has been shown that the coronary flow is increased by augmenting the cardiac output, a fact which is of fundamental importance. The most important single factor upon which cardiac output is dependent is the venous inflow into the heart. Bainbridge showed that an increased venous inflow augments the cardiac output by increasing the pulse-rate if the arterial pressure remains constant. If the arterial pressure rises appreciably, the increase in cardiac output may be accomplished

without a significant elevation of pulse-rate. Any elevation in abdominal pressure will increase the venous return from below the diaphragm to the heart. This increase is brought about by the excursion of the diaphragm in inspiration, with a simultaneous increase in negative pressure within the thorax. This latter phenomenon is largely responsible for the filling of the right auricle. Thus it follows that any amplification of diaphragmatic excursion will enhance venous return to the heart, as will a constantly augmented intra-abdominal pressure. This is accomplished in our patients by an elastic belt, which exerts a constant pressure on the abdomen but which varies with the stage of respiration. We have observed uniformly by fluoroscopy an increase in the diaphragmatic excursion of patients when their abdomens are supported. This is further shown by noting a definite increase in the respired air over a five minute period in almost all patients studied (Table 1). This determination is made with the patient in the standing position, with and without a belt, by means of a flowmeter which is connected to a tightly fitting mask over the nose and mouth.

According to Grollman and Starling, there is a definite qualitative relationship between cardiac output and velocity of blood flow. Thus any increase in velocity of blood-flow is indicative of an increased cardiac output, providing certain potential variables are unchanged. The most important of these variables is the changeability of the cross-sectional area of the vascular bed. Thus, if the cross-section is not changed, any change in circulation time should be indicative of a change in cardiac output. Circulation times were determined in many patients with postural defects and myocardial disease, who were being treated by abdominal support (Table 2). These determinations were made using decholin. The procedure was as follows: The patient stood erect with his belt in place. The decholin was injected into a vein in the right antecubital fossa at the level of the third rib, and the time of its arrival at the tongue was noted on a stopwatch. The needle was left in place, and the belt was quickly removed. As soon as the taste had left the mouth, a second circulation time was noted. In 18 of the 19

consecutive patients whose findings are shown, a material increase in blood velocity was found. This increase varied from 8 to 41 per cent. The 13th patient had reduced his weight to normal at the time of study, so that his belt was no longer exerting any appreciable compression of the abdomen. Each of the other

TABLE 1

Tidal air—volume per respiration

(Patients standing)

Case	Increase with belt	Decrease with belt	Remarks
1	X		
2	X		
3	X		
4	X		
5	X		
6	X		
7		X	Respiratory rate increased with belt
8	X		
9		X	Respiratory rate and total air in 5 minutes increased
10	X		
11		X	Respiratory rate and total air in 5 minutes increased
12		X	Respiratory rate and total air in 5 minutes increased
13	X		
14	X		
15	X		
16	X		
17	X		
18	X		
19	X		

Under the fluoroscope, the diaphragmatic excursion was noted to increase with abdominal support in all cases.

patients was studied immediately following his initial examination.

Cardiac output is obviously related to blood-pressure, as well as to pulse rate. It is generally agreed that, other variables being unchanged (chief of which is the cross-section of the vascular bed), the product of the pulse pressure and pulse rate is a rough index of cardiac output. As stated above, coronary flow

varies directly with cardiac output. Within certain limits, it also varies directly with the blood pressure. It has been shown that a pulse pressure of 25 mm. Hg is required to maintain a stroke volume output of 55 c.c. when the diastolic pressure is

TABLE 2

*Circulation time**

(In seconds)

Case	Standing without belt	Standing with belt	Decrease with belt	Increase with belt	Remarks
1	51	29.6	21.4		
2	22	14	8.0		
3	32.2	21.2	11.0		
4	16.2	15	1.2		
5	No end point	20.1			**
6	20.4	17	3.4		
7	22	17	5		
8	22.6	17.4	5.2		
11	No end point	21.2			**
12	16	16			
13	21	22		1	Treated 4 mo. when studied
14	22.6	17.6	5		
15	No end point	26			**
16	14.8	13.8	1		
17	18.8	16.4	2.4		
18	15.5	12	3.5		
19	22.8	10.2	12.6		

* 4 c.c. decholin used for injection which was done into either right or left antecubital fossa with the arm at the level of the 3rd interspace. First determination done with belt on, immediately after which the belt was removed and the procedure repeated without withdrawing the needle. The patients were standing.

** In those cases with no end point without the belt, the absence of results was probably due to a prolonged time because of dilution and slowing of the decholin in the pulmonary circulation, as suggested by the work of Hamilton and Cannon with radioactive sodium chloride (unpublished data). Such an occurrence would militate against enough decholin reaching the tongue within a given time to stimulate the end-organs of taste.

80 mm. Hg. Also, a considerable output is impossible at a high diastolic pressure, even with high pulse pressure. This is well shown by the findings in hypertension. The blood pressure of a normal individual falls immediately when the position of the body is changed from supine to erect. This is rapidly readjusted,

however, usually in a few seconds. In the type of patient we have been studying, the blood pressure falls as expected, but frequently to an astonishing degree. The pulse pressure also

TABLE 3

Pulse pressure and pulse rate studies

(Pulse pressure in mm. Hg)

Case	Lying		Standing without belt		Standing with belt		Standing without belt	Standing with belt	Standing with belt	
	P.P.	P.R.	P.P.	P.R.	P.P.	P.R.	P.P.×P.R.	P.P.×P.R.	Increase in P.P. × P.R.	Decrease in P.P. × P.R.
1	60	68	?37*	74	27*	76	2,738	2,052		X
2	32	78	15	92	17	88	1,380	1,496	X	
	36	68	17	88	25	74	1,496	1,850	X	
3	40	68	40	76	51	68	3,040	3,468	X	
4	50	78	11	120	23	102	1,320	2,346	X	
5	36	80	15	92	27	88	1,380	2,375	X	
6	54	74	30	82	38	78	2,460	2,954	X	
7	72	52	?48*	62	42	60	2,976	2,520		X
8	30	76	49	80	57	76	3,920	4,332	X	
9	74	72	57	80	59	78	4,560	4,602	X	
10	50	64	31	86	35	78	2,666	2,730	X	
11	48	74	?16	78	37	76	1,216	2,812	X	
12	40	64	20	90	25	90	1,800	2,250	X	
13	82	60	46	70	57	68	3,220	3,876	X	
14	42	72	5	100	16	98	500	1,568	X	
15	38	80	21	102	27	96	2,142	2,592	X	
16	52	88	70*	96*	58*	88*	6,720	5,104		X
17	50	84	21	96	39	88	2,016	3,432	X	
18	40	92	18	100	39	94	1,800	3,666	X	
19	54	70	22	86	49	82	1,892	4,018	X	

* Decreased pulse pressure with belt. In the 1st and 2nd cases the value of the pulse pressure with the patient standing without the belt was questionable, owing to dull diastolic end-points. The 2nd patient had marked hypertension (B.P. 180/126).

In all other cases there was an increase in pulse pressure with the belt, and in all but the 1st case, a decrease in pulse rate with the belt.

Determinations done over 5 minute period and averaged.

decreases. Furthermore, the low levels are not readjusted, but remain low as long as the patient stands. Thus another factor which militates against an adequate coronary flow comes into play. We have observed that this abnormal mechanism is

uniformly held in abeyance in our patients by a belt. With three exceptions in the 19 consecutive cases studied and included in Table 3, a definite increase in the product of pulse-pressure times pulse-rate was noted after the application of the belt. In addition, the blood-pressure was maintained at more nearly the level that had been noted in the reclining position. It has been pointed out that the intensity of the third phase of the Korotkow sounds, as heard below the cuff during blood-pressure determinations, may serve as a qualitative indication of the cardiac output. Soft tones indicate a low output, while tones of high intensity accompany a high output. We have observed that the application of a belt causes a marked intensification of these sounds in our patients. In fact, it is quite difficult to judge a diastolic pressure accurately in some of them while their abdomens are unsupported. This uncertainty of determination of diastolic pressure was especially marked in the two subjects whose pulse-pressure—pulse-rate product failed to show an increase with the belt.

So far, we have not attempted to determine accurately the cardiac output in these patients. We have not had the experience or skill to do so, but we hope to add such data during the coming year.

We mentioned earlier our original idea that the relief afforded to our patients with Heberden's angina by wearing an elastic abdominal belt was the result of an improved filling of the heart. This apparent improved cardiac filling has been observed repeatedly and consistently by fluoroscopy. Following the application of abdominal support, it is noted that the systolic excursions are markedly increased in amplitude. This is visual confirmation of the conception that the cardiac output is altered when a belt is worn.

We have attempted to show in what respect the circulatory efficiency in our patients is improved by supporting the abdomen. While the recognition of these changes is important, and justifies our therapeutic approach to the problem of angina pectoris, it is only half the story. The other half is the uniformity of therapeutic results. Our cases have ranged from patients whose

ambulatory activity was either slightly, moderately or markedly restricted by pain, to those who were completely bedridden. We have attempted to convert exercise-tolerance to terms of distance walked at a military pace before the onset of angina, with and without an abdominal belt. In not one single instance has a patient failed to gain material relief if he followed directions, and many of our patients have been able to return to a life of reasonably moderate activity without pain. We have personally seen nearly two hundred patients who have benefited from this treatment during the past four years. We have observed that reduction of weight, which is a cardinal principle of treatment, has often served to bring about relief promptly after the patient has started to wear a belt. This in itself is suggestive evidence that the removal of an abnormal accumulation of dead weight, placed so strategically that it hinders normal diaphragmatic excursion and the development of optimal negative intrathoracic and positive intra-abdominal pressure, will augment coronary flow and cardiac output.

We have also observed that some types of cardiac irregularities have been relieved,—chiefly extrasystoles but occasionally paroxysmal tachycardias. Some changes are also observed in the electrocardiograms when the abdomen is supported. Cerebral symptoms are likewise benefited.

It is suggested that prevention of coronary insufficiency is possible by controlling obesity and supporting the diaphragm in potential anginal subjects. After symptoms have appeared, relief is not only possible but is uniformly obtained, even in the most severe types.

The support should be adjusted to secure the most complete motion of the diaphragm, preferably under the fluoroscope. The belt is not worn at night. A simple rubber or other elastic belt may be worn when taking a shower-bath.

SUMMARY

A new method for the treatment of Heberden's angina is described. It is based on the assumption that relative anoxemia to some part of the myocardium or base of the aorta initiates

the pain. It can be demonstrated that faulty filling of the heart leads to inadequate output of blood during systole, and it is assumed that this results in an inadequate supply of oxygen reaching the vulnerable tissues. The chief disturbance in nearly all patients is associated with faulty motion of the diaphragm, which prevents it from performing its important function of returning blood to the heart.

The use of an elastic and supporting belt is of great value in restoring the function of the diaphragm. Dietary measures that reduce the excess abdominal accumulation of fat and restore the normal postural balances, are also important but of secondary value. When the excess weight has been reduced, postural exercises are of value. Reduction in weight may require many months to accomplish, but proper abdominal support will give prompt relief and may aid, through continual local massage, to remove excess fat from the abdominal region.

Proceedings of the College and its Sections

Proceedings of the College

March 1, 1939: Castle, W. B. The Diagnosis and Treatment of Anemia.† (*Mary Scott Newbold Lecture XLII*)

April 5, 1939: Beck, Claude S. The Surgical Approach to Diseases of the Heart. (*Mary Scott Newbold Lecture XLIII*)

May 3, 1939: Kerr, William J. A New Approach to the Etiology and Treatment of Angina Pectoris.† (*Mary Scott Newbold Lecture XLIV*)

Public Lectures

January 20, 1939: Muller, George P. Surgical Trends and Medical Progress.

April 14, 1939: Bond, Earl D. The Modern Interpretation of Mental Disorders.

Proceedings of the Sections

SECTION ON GENERAL MEDICINE

Regular Meeting, April 24, 1939

Phrenic Nerve Interruption in Pulmonary Tuberculosis. J. W. Cutler,* M.D.

The Use of Physical Therapy in the Treatment of Heart Disease. Maurice S. Jacobs, M.D.

Typhus and Rocky Mountain Spotted Fever in Pennsylvania. Harrison F. Flippin, M.D.

The Use of Vitamin B_1 in Rest Pain of Ischemic Origin. Meyer Naide,* M.D.

†Printed in this issue.

* *By invitation.*

Regular Meeting, May 22, 1939

The Use of Magnesium Sulphate in the Measurement of Circulation Time.[1] Mitchell Bernstein,* M.D., and Samuel Simkins,* M.D.

Analyses of Two Hundred Patients Examined Gastroscopically. C. Wilmer Wirts, Jr.,* M.D.

Sudden Heart Changes in So-called Acute Indigestion: Experimental and Clinical Observations. Lester M. Morrison,* M.D.

An Intestinal Method for Controlled Body Dehydration and Hemo-lavage. Harry Shay,* M.D., and J. Gershon-Cohen,* M.D.

SECTION ON MEDICAL HISTORY

Regular Meeting, March 13, 1939

Bernardino Ramazzini, Founder of Industrial Medicine. Leopold Vaccaro,* M.D.

Sir Joshua Reynolds and His Blindness and Death. Burton Chance, M.D.

Medical History in the Undergraduate Curriculum.[2] William G. Leaman, M.D.

April 3, 1939[3]

Preventive Medicine in the Bible and Talmud. Maurice S. Jacobs, M.D. (*Printed in this issue.*)

Preventive Medicine in the Middle Ages. Owsei Temkin,* M.D.

Modern Advances in Preventive Medicine. Arthur P. Hitchens, M.D., Lt. Col., M.C., U. S. A.

Regular Meeting, May 8, 1939

Karl Sudhoff, 1853–1938. Edward B. Krumbhaar, M.D. (*Printed in this issue.*)

[1] *Am. Heart J.*, 1939, **17**, 218–37.

* *By invitation.*

[2] *J. A. M. A.*, May 27, 1939, **112**, 2221–3.

[3] Joint meeting with the Section on Public Health, Preventive and Industrial Medicine.

An Athenian's Essay on Hippocrates. Hilton S. Read, M.D.

The Resurrection of 'Pile'. Joseph McFarland, M.D. (*To be printed in a subsequent issue.*)

The History of the Henry Phipps Institute. Charles J. Hatfield, M.D.

SECTION ON OPHTHALMOLOGY[4]

Regular Meeting, March 16, 1939

The Determination of Sulphanilamide in the Aqueous and Vitreous Following Administration. Willard G. Mengel,* M.D.

Exophthalmos Due to Arteriovenous Aneurysm: A Case Report. Stirling S. McNair,* M.D.

Removal of Orbital Tumors. John H. Dunnington,* M.D.

Regular Meeting, April 20, 1939

Chevalier Taylor and His Works in the Library of the College. Burton Chance, M.D.

The Analysis of Operative Results in Concomitant Convergent Strabismus. Glen G. Gibson,* M.D.

Hemeralopia Dark Adaptation and Glaucoma. Jacob B. Feldman,* M.D.

The Clinical Value of Horizontal Plane of Eyes. S. Weir Newmayer,* M.D.

SECTION ON OTOLARYNGOLOGY[5]

March 15, 1939[6]

Speech Hearing. Douglas Macfarlan,* M.D.

Sensitization Reactions as Observed Microscopically in the Living Mammal: *Introduction*, Harry P. Schenck, M.D.; *Findings*, Richard G. Abell,* Ph.D.; *Method*, Eliot R. Clark, M.D., and Eleanor Linton Clark.*

[4] The proceedings of this Section are abstracted in the *American Journal of Ophthalmology* and the *Archives of Ophthalmology*.

* *By invitation.*

[5] The proceedings of this Section are abstracted in the *Archives of Otolaryngology*.

[6] Joint meeting with the Section on Otolaryngology of the New York Academy of Medicine.

Regular Meeting, April 19, 1939

Some Unusual Neurological Conditions Secondary to Diseases of the Temporal Bone and the Paranasal Sinuses. Joseph C. Yaskin, M.D.

SECTION ON PUBLIC HEALTH, PREVENTIVE AND INDUSTRIAL MEDICINE

April 3, 1939

(Joint meeting with the Section on Medical History. For program see above under the latter Section)

Preventive Medicine in the Bible and Talmud*

By Maurice S. Jacobs, M.D.

Associate in Medicine, Temple University School of Medicine, Fellow of The College of Physicians of Philadelphia

The concept which one has of the Bible depends in large measure upon his knowledge of its contents, upon his own intellectual attainments along other cultural lines and upon his emotional reaction to this source book as a "legendary historic narrative." H. G. Wells has described its contents as "the most remarkable collection of ancient documents in the world." From the pages of the Old Testament it is possible to lift out and present in critical review those phases of medicine that are pertinent to our presentation.

Because lack of time will not permit me to cover the field in its entirety an attempt will be made to give a broad view of the subject. Let us then turn the pages of history back about thirty centuries, to the time of Moses and the Exodus of the Jews from Egypt. Prior to this the Jews had lived in Egypt for over two-hundred years and had naturally imbibed some of its culture.

Thus we find that when Moses was brought up in the household of the Pharaoh, he was instructed in all the wisdom of the Egyptians. In this manner, it is natural to assume, he became familiar with what was known about medicine, however elementary and however steeped in superstition it was. Fundamentals in sanitary and state medicine probably came before his eye and he thus obtained his first ideas on the prevention of disease. In this same position, as a member of the royal family, he acquired a knowledge of statecraft; he saw the internal machinery of government and the need for laws to govern a community. During his pastoral life in Midian he acquired first hand information about the tribal

* Read before The College of Physicians of Philadelphia, the Section on Medical History, April 3, 1939.

laws, customs and habits of the desert. Here he studied nature, always keenly observant of eveything about him. By closely watching the habits of the wild and domestic fauna of the districts he was able to make deductions as to what was fit and what was unfit for human food.

Further, by closely watching his flocks he even learnt some principles of eugenics, by noting the bad effects of in-breeding, which knowledge he was to use later in his laws on marriage.

It is obvious that the knowledge about medicine was nevertheless very meager. The Old Testament teaches us that disease is an expression of the "wrath of God, to be removed only by moral reform, prayers and sacrifice; and it is God who confers both health and disease." Besides this, the people in general, being primitive, were superstitious and could be made to carry out only those injunctions which had a religious connotation. Howsoever Moses acquired his knowledge of disease and disease prevention, it was only through an appeal to his people's religious sense that he could enforce those laws which he felt were necessary for their well-being and protection. To have made any attempt to teach the children of Israel even the most elementary principles of hygiene would have been impossible. Although his people, when they left Egypt, were essentially the same as an army on the march, he could not issue "Routine Orders" as is done in an army today. Accordingly, he appealed to primitive instinct, their religious beliefs. One can readily see that the religious sense is evolved long before the sanitary sense: hence it might truthfully be said, not that "cleanliness is next to Godliness," but, rather, that "Godliness comes before cleanliness."

There are seven essentials of preventive medicine, both in civil and military life, which, according to Captain Percival Wood,[1] may be enumerated as follows: 1. An adequate supply of pure water. 2. Preservation of food from all contamination (by infectious agents, flies, road-dust, decomposition, etc.). 3. Prompt and effective disposal of all decomposable matter (manure, soapy water, kitchen refuse, etc.). 4. Personal cleanliness (absence of

[1] *Moses, the founder of preventive medicine.* London, Soc. for promoting Christian Knowledge, 1920. Pp. 3–4.

vermin). 5. An efficient organisation for the control of infectious disease. 6. Avoidance of overcrowding. 7. An adequate and suitable dietary.

It was such essentials as these that formed the basis of the Mosaic Code, as we shall point out.

In any well-organized community one of the first public functions to be performed is the taking of a census. Accordingly we find this being done, . . . "when thou takest the sum of the children of Israel." According to this census there were over 600,000 adults.

Because he was not satisfied with the medical art of his day, Moses determined to found a better, more rational system. He believed that it was better to prevent disease, and upon these grounds founded the system of hygiene or preventive medicine. Public health officials were, therefore, appointed. These were the priests, who were taught the principles of contagion, isolation and disinfection. He organized a staff of officials who were "able men, reliable men—men who could not be bribed—men who could be taught and who would practice their profession with the greatest skill and precision." (*Ex.* 18:21).

As has been indicated the population of the Israelites in the wilderness was approximately 600,000. Accordingly Moses needed a large organization to take care of their health needs. This was set up as follows: For every thousand persons he appointed a chief. Thus there were 600 chiefs. For every hundred persons, an assistant chief—6,000 assistant chiefs. A supervisor was responsible for 50 persons—12,000 supervisors; and a captain for every 10 persons—60,000 captains. These officials constituted the priesthood. As the administration of Moses consisted of only two departments—the ritual and the legal (which included the medical)—the officers that enforced all the laws and practiced the religious rites were selected from this great group of officials. The health officers were taught the laws of the state and were given full power to enforce them.

Because cleanliness was the keystone in the arch of the Mosaic Code, let us look into the methods used to ensure this. Stress was laid on personal cleanliness. Above all else, strict rules were

laid down relative to the washing of the hands, the feet, and the entire body. When we recall that even today there are whole nations who do not resort to the most fundamental principles of bathing we begin to grasp the importance of these rules laid down over 3000 years ago.

It should be recalled that when these injunctions were promulgated the people of Israel were in camps, frequently on the march and in general behaved as a nomadic race. Second to personal cleanliness came the instructions relating to the camp itself: "Keep your house clean, because I the Lord am in your midst." And, finally, the most stringent rules as to cleanliness revolved about the Altar or Tabernacle where the people prayed. Not only did they have to be personally clean, but their clothes had to be clean, in order to enter.

What might be termed "personal hygiene" was in later years expanded. The Rabbis enjoined upon the Jew to perform ablutions on rising, also before morning and evening prayer, before meals, and on other occasions. Periodically he must bathe. Further, before he can offer up prayer, the room must be cleansed and all impurities cleared away.

Cleanliness and godliness were very near akin in those days; cleanliness of mind was not to be attained without a clean body. In later, pagan days this attitude was recognised in the phrase "mens sana in corpore sano," and a comparison may also be made with the custom of immersion in baptism.

But personal hygiene means much more than personal ablutions, and careful directions are given for certain normal physiological conditions. Attention is paid, for example, to the purification after child-birth, and minute injunctions are laid down for the hygiene of conditions peculiar to women.

There is one other matter to which reference must be made and that is circumcision. This was not a Mosaic institution, nor was it by any means a practice confined to the older Hebrews. It was indeed very widespread and of great antiquity, being regarded at first apparently as social rather than religious or hygienic. The significance seems to have been that it was an initiation into manhood, for in the majority of tribes it was not performed until

about the age of puberty; an uncircumcised youth was not a full member of his tribe, nor was he allowed to marry. But there was this distinctive feature about circumcision among the Hebrews; it was peformed in infancy, at the age of eight days, which is more humane and more hygienic. With the Hebrews again, circumcision was given a definitely religious character, though long before the age of Moses. But whatever be the origins of circumcision, it remains a fact that it is a health measure, beneficial in many ways that need not be specified here.

Soldiers returning from the wars were isolated for a period of seven consecutive days before they were admitted into the camp. All that slew an enemy or that had come in contact with a fallen combatant had to be disinfected with the disinfecting solution. Their clothes and booty, consisting of wooden articles, skins, or trinkets made of ivory, etc., were to be disinfected. Articles of gold, silver, copper, iron, tin or lead were scoured and polished and all tarnish and rust removed from them and made to look like new. All articles that could withstand fire were to be sterilized, "passed through the fire," and also disinfected with the disinfectant solution; those articles that could not withstand fire, such as glass, bottles, etc. (except earthenware, which must be destroyed) were to be thoroughly washed in water. On the seventh day the clothes, as well as the entire body, were washed, after which the soldier was eligible to enter the innermost camp or camp of the Tabernacle.

There were rules to govern the disposition of animals during warfare: Carcasses of non-kosher as well as kosher animals that died a natural death were considered capable of contaminating; bones, horns, hoofs, hides not so. Modern medicine, on the contrary, recognizes the possibility of the spread of anthrax through contact with hides of infected cattle. Raiment, skins, sacks, wooden and all useful articles that came in contact with the carcass of a non-kosher animal were not to remain overnight without being thoroughly washed in water.

The instructions even went so far as to include inanimate objects. Thus we are told: Earthenware becomes contaminated if the "unclean object" happens to be inside of it; and all that is

contained therein becomes contaminated as well. The air becomes polluted by it. Such contaminated earthenware can never be cleansed. An earthern vessel in which the meat of a sacrificed animal is boiled shall be destroyed; a copper vessel, however, after it is rinsed well in water and scoured, may be used again. The reason for this is that an earthen vessel, by means of its pores, absorbs into itself minute particles of the material contained therein; these cannot be removed, no matter how thoroughly rinsed or scoured; a copper vessel, if thoroughly rinsed and well scoured (polished), is free from any particles after its contents have been removed.

Second only in importance to personal hygiene was the organization for the control of infectious diseases. Since diseases were naturally not named as we know them today we can only infer from their descriptions their analogies or equivalents of today. It must not be forgotten that even as late as the 15th & 16th centuries many diseases were simply called Fevers. Even such common diseases as scarlet fever and measles were not differentiated till Sydenham's famous description in 1675. It is little wonder then that only generic terms like plagues, pestilences, fevers, rashes, fluxes and issues are the only descriptive terms that have come down to us. Nevertheless, it is commonly accepted that such diseases as leprosy and venereal infections existed. Greater, rather, is the wonder that their contagiousness should have been recognized and stringent laws laid down for their diagnosis and prevention. In all of this we still see the marked influence of the religious aspect of disease. Thus, to be ill was to have sinned, to have sinned meant to be unclean, and to be unclean meant isolation.

For purposes of isolation the camp or community was divided into three categories. Those people found to be ill of a very contagious disease were sent outside, beyond the third camp; those ill of a less serious infection, e.g., urethral discharge, outside the second camp; whilst those of only minor contagion, e.g. contact with a corpse, were sent outside the first camp. In addition there were two varieties of isolation: Temporary, where the patient was shut in his tent whenever the case was doubtful or where

there was a history of exposure to disease or an unclean object. Here, then, we have the first illustration of quarantine not because of actual presence of a contagious disease, but where it was only suspected. This too, if you please, 2500 years before Ragusa and Marseilles, the cities which first practised modern detention for contagious diseases and from whose detention of suspected ships for forty days we get our name quarantine. If after one or more periods of seven days each, the health-officer (priest) found that the disease was progressing, the patient was then declared unclean and sent outside the camp, as mentioned above, for isolation until cured.

In addition to leprosy there are the strictest regulations relating to urethral and other body discharges. So stringent were the rules in cases of gonorrhea, that not only was the person regarded as unclean, but also his garments and everything with which he came in contact, even to the saddle upon which he rode.

Although, as has been stated, it is impossible to indentify all the diseases mentioned with their latter-day equivalents, if indeed these are known, nevertheless it would seem that certain of the "plagues" have a rather definite connotation. Thus the plague of Baal-Peor (mentioned in *Numbers* xxv. 9) was undoubtedly of venereal origin. It is recorded that as a result of the plague 24,000 persons perished. Is it any wonder then that such stringent regulations were laid down for their prevention? Wood has pointed out that that disease in which the people were afflicted with "Emerods" as mentioned in 1. *Samuel*, was probably bubonic plague, and color is lent to this suggestion by the mention of this disease in connection with the statement, "... and the mice died and marred the land."

Another important link in the proper protection of the people against infectious diseases was the prompt and effective disposal of all decomposable matter, of all refuse and more especially of all human excreta. It is a little difficult for us living in sanitary surroundings today to visualize what a task it was to arrange for proper sewage disposal in a primitive horde of tribal herdsman more or less constantly on the march during forty years in the wilderness.

Sewage disposal was unknown to Moses. Even if it had been, it would have been of no use to a wandering race. Something to take its place was needed. Moses, therefore, advocated the system of waste-disposal at a site well beyond the limits of the third camp. This included the waste materials of the animal sacrifices, disposition of human excreta, and burial of the dead.

This complete removal and immediate destruction by fire of obnoxious debris was an efficacious sanitary procedure for the prevention of offensive sights, of disease-breeding material, of putrefactive odors, and for the maintenance and preservation of the public health. If the removal had not been a state function and had been permitted to remain a private one, it probably would not have been carried out as efficiently. Therefore, removal was made imperative and a state function, carried out by a state official.

The strict enforcement of sanitary rules was effected by the official dictum: "For the Lord, thy God, walketh in the midst of thy camp, therefore shall it be immaculate. Do not contaminate the earth where ye dwell, for I dwell there also; I am the Lord that dwells among the children of Israel."

Just as the waste material and excreta of animals were disposed of outside of the camp, so human excreta were treated. "Covering the excreta," and appointing a special place outside the camp for depositing it, were strict health regulations. How more like the modern treatment in present warfare, where the spading-tool is part of the equipment of every infantry-man!

Included under the heading of removal of waste and unhygienic material was the disposal or burial of the dead. The fact that the blood was considered "the life" led to the following order: "Whosoever taketh a beast or a fowl for food, the blood that the animals lose shall be covered with earth": that is, it should be buried. If a man be hanged, "his body shall not remain all night upon the tree, but thou shalt surely bury him the same day, that thou defile not the land": this is emphasized because dead bodies decompose and become offensive very rapidly in warm climates, and if not speedily removed become a source of disease.

The Hebrew funeral usually took place not later than twenty-

four hours after death, to prevent widespread "uncleanliness" from contact with the dead body, its tent, etc., and to remove as speedily as possible a sure source of contamination.

It needs no great exposition to demonstrate that public health is the sum total of personal hygiene. Those who keep their own bodies, houses, clothing, etc., clean are the ones who appreciate clean streets, clean communities, and clean countries. That is why personal hygiene of cleanliness is so fully detailed in the Mosaic code. The camp, the tabernacle, the individual tents of the Israelites, were but a sanitary reflection of their own personal make-up. Contrariwise, the lack of cleanliness, the failure to effect measures for proper disposition of refuse, of sewage etc., leads inevitably and irrevocably to disease.

Health bulletins, listing procedures for special conditions, specifying contaminations, and outlining rules and regulations were issued to the populace. Thus, spitting was prohibited and anybody who had been in contact with sputum was regarded as unclean for seven days. Spitting is prohibited in our trolley cars and public places and is punishable by fine. I wonder if this is ever enforced!

We come now to the preservation of food against contamination. The dietary laws are based on several factors, which include rules for the selection, sanitary preparation and eating of various foods. As to the proper selection of foods, the chief feature included the admonition: "Do not eat anything repulsive." Food for human consumption was accordingly divided into that which was clean or fit (kosher) and that which was unclean or unfit (traypho). In addition, there are chapters in the Bible which teach the benefits of moderation and the dangers of overindulgence. Centuries later these same principles were enlarged and embodied in the famous *Regimen Sanitatis* of Maimonides.

Wise regulations against eating fats, blood, and excess of meats were laid down; wise because in the subtropical countries in which the Israelites lived excesses of fat would lead to corpulence and hence to laziness. "Nobody loves a fat man" might well have been a favorite saying of Moses. He legislated also against

overindulgence not only in food but in the use of alcohol as well, excesses of this sort leading to crimes against society.

Moses was well aware of the four generic terms for food constituents—proteins, fats, carbohydrates and starches—and foods were divided accordingly. Furthermore, the dietary code in listing the restrictive measures mentions the four classes of animals that may be used as foods—mammals, birds, fish and insects. The kosher quadrupeds or mammals must possess these three characteristics, combined: cloven hoof, parted hoof, and cudchewing. Such animals are herbivorous (grass eaters). The flesh of such beasts is wholesome, nutritious, edible, and palatable. The kosher fish are those that have fins and scales; these, too, are vegetable or seaweed-eaters, and their meat is wholesome. In the group of birds, some twenty unclean birds are specified, but no general procedure is laid down. This defect is supplied by the Talmud, which gives five general characteristics that identify a kosher bird: (a) it is not a bird of prey; (b) in addition to its front toes, it must have a posterior one; (c) it must have a crop or craw; (d) its maw or stomach must be of double skin that can be easily separated; (e) it must catch its food, lay it on the ground and peck it with its beak, instead of ensnaring its food, pressing it with the foot and tearing it asunder.

The kosher insects are characterized by "leaping legs above their feet"—long, kangaroo-like hind legs; these insects are herbivorous. No shellfish were allowed to be eaten, and no reptiles.

Excluded from the kosher lists are the voracious, carnivorous and predatory animals and fish, and those living on dead or putrid matter. Their flesh is usually tough, indigestible, and subject to parasites. Excluded also from the kosher lists are kosher animals that have died, the reason being that they may have been victims of a communicable disease (such as tuberculosis in a cow) which might affect the one eating such meat. Forbidden meat was also "flesh (even from a kosher animal) that was torn by the beasts of the field." Such flesh may be contaminated by the hydrophobia of an enraged animal (dog, wolf, or fox). Those who had eaten

of such meat had to bathe themselves, wash their clothes thoroughly, and be segregated for twenty-four hours: if no symptoms appeared, they might return to the camp and not menace the health of their fellow citizens.

In the listing of the kosher or clean and non-kosher or unclean animals it will be noted that in some cases names are specified, and, in others, species or genera are mentioned. Such an instance is the mouse "according to its kind;" thus mouse, here, is a generic term and includes not only the ordinary mouse, but any small rodent such as the rat, dormouse, guinea pig, etc. Another example is the red kite, indicating that this is a generic term for various kinds of carrion birds; the same with raven, this embracing several species. The great 11th-century commentator Rashi says that when the members of a species of beasts, fish, or birds are enumerated by name, that species is a limited one; if, for example, names of unclean or non-kosher birds are listed, that means that the clean or kosher birds far outnumber them. It will be noted that the text lists the bat last among the birds, because there was some difficuly in determining whether it is a bird or a mammal, a sufficient reason for its exclusion from the edible animals.

In 1846, Joseph Leidy discovered the parasite nematode *trichina spiralis* in American pork when cutting a cold ham sandwich, which led to the conclusion that man might become infected by eating raw pork. In a country where extremes of heat prevailed, anyone who knows pork would have no difficulty in realizing that indiscriminate eating of it is fraught with many dangers. The trichina was doubtless as active then as it is now. In the days of old, when there was no microscope and when medical analysis was unknown, the ills from eating pork would not be diagnosed as trichinosis; they would be traced, however, and quite naturally, directly to the results of eating pork.

The swine, therefore, early became unclean. The rodents were also placed in the same class as the swine, on account of their transmission of diseases fatal to men. The rats that carry the bacillus pestis and cause the plague, the mouse that carries the fleas that cause typhus, are but two known carriers of disease.

Recently a new disease was described: tularemia, a plaguelike disease of rodents (squirrels, rabbits) was first described in 1911, by McCoy of the United States Public Health Service, who found this disease in the squirrels of Tulare County, California. The fatal sequelae of this disease were probably recognized in olden days, though not as tularemia, but yet were traced to the handling or preparing of these animals. More and more of the medical knowledge contained in the Bible will come to light as we explore the mysteries of the past; for the Great Teacher prophesied that "later and future generations will be amazed and will attempt to interpret the universal epidemics and the puzzling diseases which the ancient Israelites had lived through; and scholars in all parts of the world will search for an explanation of those great scourges." (*Deut.* 29:21, 23). Even in recent times we have seen minor outbreaks of typhoid fever that could be traced directly to the eating of oysters from infected beds.

Reference has already been made to the cautions issued against alcoholic beverages; on the other hand, we find that milk was recommended as a beneficent food. Naturally we do not know what Moses knew or suspected about calcium or vitamins, but he did know that milk was of value in building strong white teeth. We read in Genesis, in one and the same verse, "Wine makes the eyes red, and milk makes the teeth white."

In addition to the broad generalities already referred to, it was necessary to guard against the transmission of infectious diseases through foods. This was accomplished by laws which urged that food and food-containers be covered and thus protected against contamination. The same and even more stringent orders were issued relating to refuse and garbage. One need hardly go back more than a few decades to find even these simple rules ignored in our community.

Another safeguard against food poisoning from decomposition is seen in the injunction against eating left-over foods. You need but recall that this was long before refrigeration and that we are talking about a country in the subtropics.

Further safeguards against eating foods that might be contaminated have come down to us in the ritual killing of animals

for food by the *Shochet,* who is trained in method of painless death —the real Lord High Executioner of the cows and chickens. But this is not all. Before any of these meats are used for human consumption, they are inspected. And if, for example, the cow's lungs show evidence of adhesions to the pleura, the cow is not used for food. Surely this would seem to indicate that some knowledge of the presence of pulmonary diseases was known to our later Talmudic scholars by whom these tenets are first pronounced.

Little has been said about the water supply. The code recognized the importance of a pure and adequate source of water. To this end Moses would frequently send scouts to search for such a site prior to their migration from place to place during their stay in the wilderness. The importance of boiling water, and, in fact, of fire as a whole for sterilization purposes, was well recognized. In fact it may be mentioned in passing that one rationalization of the Ten Plagues begins with the supposition that when the waters of the Nile were supposed to have turned to blood a polluted water supply was indicated.

When the scouts went out to search for new camping places they were instructed also to find a location that was high, that had sufficient sunlight and that was big enough to prevent over-crowding. Present day civil as well as military men realize the importance of this, though frequently they can do nothing about it. Yet we realize that the more crowded the quarters the greater the danger of contagious diseases. Only a year or two ago, Dr. G. C. Ruhland, the Director of Health of Washington, D. C., in speaking about the greater incidence of tuberculosis among the colored people in his city mentioned over-crowding as the chief cause. The same holds true in our own city, where the incidence of the disease is relatively about five times as great among the colored as among the white population. Over-crowding is the chief, if not the sole factor.

Finally, it might be interesting to speculate upon certain of the provisions instituted in this community for the care of the young and the aged. Whilst not actually belonging under the heading of preventive medicine, they nevertheless rightfully should be

included in any discussion of the broader aspects of public health.

What are the facts? We find, for example, that there was no child-labor problem. In fact, not until one was 20 years of age was he allowed to work, and in some of the tribes not until he became 30. Prior to this time he was too young: he still had to study and to serve his apprenticeship. And what of the other extreme? Men beyond the age of 50 were excused from hard work. Younger men took their places, while they, the older men, stayed on to instruct them, acted as watchmen and, in general, did other light duties. Nothing however is said about old-age pensions, and of course there is no mention in the Bible of a deficit in the government budget.

REFERENCES

I wish to acknowledge my debt to the following works, from which I have quoted freely without indicating, usually, the specific limits or sources of the quotations:

Brim, Charles J., *Medicine in the Bible: the Pentateuch, Torah.* New York, Froben pr., 1936.

Garrison, Fielding H., *An introduction to the history of medicine.* 4th ed. Phila. and London, Saunders, 1929.

Jacobs, Maurice S., "Circumcision," *Ann. Med. Hist.*, 3d ser., vol. 1, no. 1 (Jan., 1939), 68–73.

———"Maimonides, a modern physician," *Phi Lambda Kappa Quarterly*, April, 1935.

Preuss, Julius, *Biblisch-talmudische Medizin.* 2d ed. Berlin, Karger, 1921.

Rivers, W. H. R., *Medicine, magic, and religion.* London, Kegan Paul, Trench, Trubner & Co.; New York, Harcourt, Brace & Co., 1924.

Waxman, Meyer, *A history of Jewish literature.* New York, Bloch Pub. Co., 1930.

Wood, Percival, *Moses, the founder of preventive medicine.* London, Soc. for promoting Christian knowledge, 1920.

The Babylonian Talmud. Translated into English under the editorship of Rabbi I. Epstein. 24 vols. London, Soncino pr., 1935–9.

The Pentateuch and Rashi's commentary. Translated and annotated by the Rev. M. Rosenbaum and Dr. A. M. Silbermann. London, Shapiro, Valentine & Co., 1929.

Karl Sudhoff, 1853–1938*

By Edward B. Krumbhaar, M.D.

Professor of Pathology, School of Medicine, University of Pennsylvania; Fellow and Vice-President of The College of Physicians of Philadelphia

In the death of Karl Sudhoff last October 8th, in his 86th year, the world lost its greatest medical historian—a man who had cultivated medical history throughout his long professional career of 62 years, though for the first 28 of these it was in the intervals of a busy horseback practice at Frankfort and in the vicinity of Düsseldorf. In 1898, for instance, he prepared a masterly exhibit on the history of science; and in 1901 he helped found the German Society of Medical History, of which he was the first president. From 1901 to 1906 he published, with Magnus and Neuburger, the *Abhandlungen zur Geschichte der Medicin*, and in 1902 he founded, with Neuburger and Kahlbaum, the *Mitteilungen zur Geschichte der Medizin und der Naturwissenschaften*.

It was only in 1905 that he regretfully gave up the pleasures and remunerations of private practice (specializing in gynecology) to devote himself, full time, to the pursuit of medical history as the first director of the Institute endowed by the widow of Professor Puschmann at the University of Leipzig. Here the groundwork that he had laid in his philological studies at the Gymnasium and his life-long pursuit of his supposed ancestor, Paracelsus, served as the basis for an imposing edifice of historical research that produced desirable repercussions throughout the civilized world. It is fitting that his last article, in 1937, should have been on Paracelsus' knowledge of music. Of Sudhoff's magnificent definitive edition of Paracelsus' works, by the way, publication of Part 1 (the biological part) was completed with the appearance of the fourteenth volume, in 1933. I suppose that

* Read before The College of Physicians of Philadelphia, the Section on Medical History, May 8, 1939.

now it is doubtful if the second part, on the Paracelsian theology, will ever appear. Our own, and only, institute of the history of medicine, at Johns Hopkins, can be directly traced to Sudhoff's influence on Welch, and on Sigerist, his follower at Leipzig and our leading medical historian in this country today.

The torrent of sound historical articles that poured forth from the Institute at Leipzig and from Sudhoff's own pen cannot be detailed here.[1] We can take Garrison's word for it that his achievement "has not been approached in variety, extent and importance by that of any other medical historian of the past or present. Sudhoff has practically created the newer history of the medicine of Hellenistic Alexandria, and the Middle Ages, including the school of Salerno, of ancient balneology, dentistry and veterinary medicine, of the Paracelsian writings, of the traditional anatomy of tbe Middle Ages and of many another theme of lesser importance."[2] His strenuous denial of the American origin of European syphilis will perhaps best recall him to the Fellows of this College, that having been the subject of his address here in 1929.[3] His ability was analytical rather than synthetic; at its best in unearthing, documenting and evaluating textual evidence on distant periods of medical history. His edition of Pagel's *Einführung* owed most to these qualities.

Sudhoff's methods of investigating medical history are interesting. Far from relying mainly on the excellent library of his Institute, he emphasized the need for extensive travel in search of original material, and practiced what he preached. In the first ten years of his Institute, he made a dozen extensive journeys —mostly to Italian museums and libraries, but also to England, Austria, and various parts of Germany. Whatever he touched not only bore fruit in his own hands, but often served as a starting

[1] For a systematic list of Sudhoff's writings see *Sudhoffs Archiv für Geschichte der Medizin und der Naturwissenschaften*, Bd. 27, Heft 1 u. 2, 1934, pp. 131–186; Bd. 31, Heft 6, 1938, pp. 343–4. A valuable, though necessarily less detailed, survey of a similar sort may be found in Garrison's biographical sketch of Sudhoff in the latter's *Essays in the history of medicine*, New York, Medical Life Press, 1926.

[2] Garrison's biographical sketch (pp. ix-x) referred to in note 1 above.

[3] An abstract in English of this address was made by the author of this memoir and may be found in the *Transactions of The College of Physicians of Philadelphia*, 3d ser., **51** (1929), 352–356. [Editor's note.]

point for his assistants and students for articles which were recorded in the *Arbeiten* of the Institute and in the *Sudhoffs Archiv für Geschichte der Medizin und der Naturwissenschaften.*

It required but little association with Karl Sudhoff to realize his great personal qualities. Proud as he was of his native country, he never dreamed of giving it more than its proper credit in history, or of doing aught but present the results of his Germanic studies solely as the truth appeared to him. With the simplicity of many big men, he spoke confidently but not arrogantly, acted naturally in ways that were more naive than egotistical. I well recall how, on his first visit to my house, after a very modest lunch he unconcernedly and without ado stretched out on the sitting-room sofa for his customary postprandial nap. Majestic in appearance, with his large, full, silvered beard, he lacked only the broad-brimmed black felt hat to be one with the many earlier German scientists who imitated the Wotan costume of Wagnerian Germany. It has frequently and truly been said that Sudhoff had a masculine mind; deeds and substance counted more for him than words and form. Occasional brusqueness, then, was to be expected. A fierce defender of the truth as he saw it, and a patient and efficient searcher for it, he represents to me the best type of German investigator — with faults to be sure; but who is perfect? Shall we see such men developed by the Germany of today?

Memoir of Addinell Hewson, M.D.†

By J. Parsons Schaeffer, M.D.

Dr Addinell Hewson was born in Philadelphia, September 2, 1855, and died at his home in Bryn Mawr, October 27, 1938, after a short illness, at the age of 83 years. His was the fifth of consecutive generations of distinguished physicians and surgeons. Dr Hewson was proud of his forebears, and rightly so, and, although his own inherent qualities of appreciation and justice were constantly manifested, he always felt that he had position and honor to maintain because of a rich heritage. That he was influenced by the character and achievements of his progenitors was frequently evidenced by his pleased reference to them and by the place he gave in his office to pictures and mementoes indicative of their accomplishments and worth.

Of the first of an unbroken line of medical men, extending over a period of more than two hundred years, of whom we have a record, William Hewson, physician and apothecary of Hexham, England, who was born in the latter part of the 17th century, little is known or recorded, probably because he was eclipsed by his more prominent and distinguished second son, of the same name, born at Hexham, 1739. The younger William Hewson, the great-grandfather of the subject of this memoir, studied under his father and the celebrated Hunters, John and William, and is credited with the discovery of the lymphatic system in fishes. His memoirs on the lymphatic system in birds, fishes, and amphibious animals gained wide recognition at the time and won for him the Copley Medal in 1769, and a Fellowship in the Royal Society in 1770. In the midst of other important discoveries, William Hewson, the younger, died in 1774, at the early age of 35 years, from septicemia, following a slight wound received while dissecting.

† Read at the meeting of the College, March 1, 1939.

Thomas Tickell Hewson, the next in order and the grandfather of the late Addinell Hewson, was born in London in 1773 and was but one year old when his father, Dr William Hewson, died. Thomas' mother was an intimate friend of Benjamin Franklin and it is written that on the advice of Franklin the widow of William Hewson with her three children emigrated to Philadelphia in 1786. Her son Thomas, who was destined to become a great physician, had studied at the school of William Gilpin, near London, and had spent some time with Franklin at Passy. Soon after his arrival in Philadelphia, Thomas was admitted to the College of Philadelphia, from which he was graduated with the degree of A.B. in 1789. He studied medicine with Dr John Foulke for five years, returned to England in 1794 to continue his medical work at St. Bartholomew's Hospital and in Edinburgh. He returned to Philadelphia in 1800 and entered upon the practice of medicine.

Time and space prevent rehearsal here of the many and varied achievements of this gifted man, both as a doctor and as a public servant. He was a busy practitioner, had a number of hospital connections, translated Swediaur's *Treatise on syphilis* from the original French, was Professor of Comparative Anatomy in the Department of Natural Science of the University of Pennsylvania, rendered valuable service in the typhoid epidemic of 1817, the yellow fever epidemic of 1820, and the cholera epidemic of 1832. Harvard University honored him by bestowing an honorary M.D. degree in 1822. He was a member of leading medical and learned societies, among which was The College of Physicians of Philadelphia, whose president he was from 1835 until his death in 1848, a period of 13 years.

The eighth child of Thomas Tickell Hewson was born in Philadelphia, November 22, 1828, and was named Addinell. He was the father of our Addinell Hewson. The elder Addinell Hewson was a graduate of the University of Pennsylvania, receiving the A.B. degree in 1848, and a graduate of the Jefferson Medical College, receiving the M.D. degree in 1850. He studied later at St. Mark's Hospital and the Rotunda Hospital in Dublin and

subsequently became resident physician of the Pennsylvania Hospital in Philadelphia.

Later the elder Addinell Hewson served the Pennsylvania and other hospitals in this city and edited the American edition of Mackenzie's "Practical Treatise on Diseases of the Eye." He appears to have been one of the pioneers in the field of antiseptic surgery and it is stated that he obtained union of tissues by first intention. He was a disciple of torsion, that is, twisting the cut end of an artery to arrest hemorrhage. He invented a torsion forceps and was one of the first to make use of electricity in the practice of medicine. He is reported to have operated upon and successfully removed a bullet from the side of General George Gordon Meade shortly before the latter directed the Union forces at the Battle of Gettysburg. The elder Dr Addinell Hewson died in 1889 and was survived by his wife and six children, one of whom was the Addinell Hewson whose memory we now honor.

Addinell Hewson, the junior, was born in Philadelphia on September 2, 1855. He was the son of Dr Addinell and Rachel Macomb Wetherill Hewson and received his preliminary education at the Episcopal Academy, graduating from this preparatory school in 1872. In the autumn of the same year, he was admitted to the University of Pennsylvania, and on completion of the classical course was graduated with the A.B. degree in 1876. During his student days at the University of Pennsylvania Dr Hewson was interested in athletics. It is recorded that he held the mile track record for a period of four years, an achievement that reveals him as interested not only in the curricular side of his college life but in important extracurricular activities as well. Probably some of the fire which was his and his constant willingness to enter a fight for just cause were kindled by his early participation in athletics. In a recent publication of the University of Pennsylvania, it is recorded that Dr Addinell Hewson when a student "was the first to propose the Red and Blue as the official colors of the University." The occasion for this proposal appears to have been a track meet with Harvard and Yale at a time when Pennsylvania lacked college colors. This was deplored by the

home participants and in a heated discussion student-Hewson shouted, "Let's beat them with their own colors!" And thus the Red and Blue came into being.

For his medical studies Addinell Hewson chose the Jefferson Medical College, the Alma Mater of his father, receiving the M.D. degree with two citations in 1879. His graduation thesis was entitled "The Anatomy of the Male Urethra." He received, also, in the same year the degree of Master of Arts from the University of Pennsylvania, the title of his thesis being "The Effects of Sunlight on the Growth of Plants."

Following his graduation from the Jefferson Medical College Dr Hewson immediately began his career as a teacher of anatomy and as a surgeon. At the Jefferson Medical College he was, in order, Assistant Demonstrator of Anatomy (1879–1886); Prosector of Anatomy (1886–1889); Demonstrator of Anatomy (1889–1902); and Assistant Professor of Anatomy (1902–1905). Early, on the clinical side, Dr Hewson was dispensary surgeon at the St. Mary's Hospital (1879–1884); assistant at the Ophthalmic Clinic of the Jefferson Hospital under William Thomson and assistant in the Surgical Clinic of the elder Gross.

From 1897 to 1928, Dr Hewson was Professor of Anatomy at the Philadelphia Polyclinic and College for Graduates in Medicine, now the Post-Graduate School of Medicine of the University of Pennsylvania, becoming professor emeritus on his retirement from this Chair.

From 1917 to 1923, Dr Hewson was Professor of Anatomy and Histology in the medical and dental schools of Temple University, and from 1923 until the time of his death in October 1938, he occupied the Chair of Professor of Anatomy in the Temple University School of Dentistry.

Following his early hospital connections, Dr Hewson was physician to the Philadelphia Orphan Society (1884–1901); dispensary surgeon, Episcopal Hospital (1887–1904); surgeon, St. Timothy's (now Memorial) Hospital, Roxborough (1894–1928). At the latter hospital he was emeritus surgeon at the time of his death.

In characteristic manner and in a spirit of service, Dr Hewson

was one of the first volunteers to go to the aid of the stricken at Johnstown during the flood of 1889. He caused announcement to be made in various churches, supervised the collection of large quantities of clothing and medical supplies, organized and directed a medical unit from Philadelphia and embarked on the first relief train. Subsequently he received a certificate for distinguished service.

Dr Hewson was a member of the Philadelphia County Medical Society, Pennsylvania State Medical Society, American Medical Association, American Association of Anatomists, American Association for the Advancement of Science, Philadelphia Academy of Surgery, Fellow of the American College of Surgeons, Fellow of the College of Physicians of Philadelphia, one of the founders of the Oncologic Hospital in Philadelphia, member of the Sons of the American Revolution, of Phi Kappa Sigma and Alpha Kappa Kappa fraternities, and was a member of the Episcopal Church, serving as a vestryman. Dr Hewson was too much occupied with other work to make it possible for him to become conspicuous in the field of research; nevertheless, he was the editor of two of the American editions of Holden's "Anatomy" and contributed a number of papers to scientific and medical journals.

In concluding this memoir, it is fitting that mention should be made of probably the most outstanding service of Dr Hewson, a work that was very near his heart and to which he gave his best and most devoted efforts. For more than forty years he was actively and vitally allied with the many and varied functions of the Anatomical Board of Pennsylvania. For more than twenty-five years the writer of this memoir was associated with Dr Hewson in this work and learned to know of his sterling qualities, his ability, vibrant energy and loyalty. In the capacity of Secretary of the Board from 1899 to the time of his death, Dr Hewson, through the Executive Committee of the Board, fearlessly and efficiently, albeit with a kindliness which was not always appreciated, administered the laws pertaining to the distribution and use of unclaimed dead human bodies for scientific purposes, thereby greatly aiding in the promotion of anatomical

knowledge and the advancement of preventive and curative medicine in a fundamental manner. The medical colleges and schools, the medical profession, and the general public owe Dr Hewson a debt of gratitude for his untiring efforts in aiding in the formulation and maintenance of laws bearing on the use of unclaimed bodies in the furtherance of scientific medicine, laws that are now found to be equitable and satisfactory both to the medical profession and the general public. In this work Dr Hewson never side-stepped a duty and the Anatomical Board will greatly miss his dynamic presence, his friendliness, and his constant willingness to be of service in the promotion of better things.

On September 4, 1883, Dr Hewson was married to Miss Lucy Clabaugh, Taneytown, Maryland. Of this union there are four children, William, Ellen (Mrs. Douglas), Addinell Stevenson, and Harry M. Clabaugh. The eldest son, Dr William Hewson, a physician specializing in otolaryngology in this city, is of the sixth successive generations of doctors in the Hewson family.

Memoir of Benjamin Franklin Baer, Jr, M.D.†

By George Morris Piersol, M.D.*

The untimely death of Dr Benjamin Franklin Baer, Jr., on December 19, 1938 deprived The College of Physicians of Philadelphia of a distinguished Fellow and the medical profession of this country of one of its most outstanding ophthalmologists.

Dr Baer was born in Philadelphia on November 4, 1879. Both of his parents were remarkable for their courage, determination and capacity for hard work. His father was a distinguished surgeon and one of the pioneer gynecologists in America. The story of how he came to take up medicine was one of his son's most prized anecdotes. It seems that the elder Dr Baer started life as a retail provision merchant in Harrisburg. One day, he submitted by mail a sample of his handwriting to an expert who professed to be able to discover unsuspected abilities by the analysis of an individual's handwriting. When the reply was received stating that he possessed inherent but latent capability as a surgeon, he promptly gave up his business, came to Philadelphia and entered the Medical School of the University of Pennsylvania, from which he was graduated in 1876.

Dr Baer's mother was a Southern girl who met his father during the closing days of the Civil War, at Petersburg, Va., where he was stationed with the Federal troops. After the war, in spite of violent opposition from her Confederate family, who were determined that she should not marry a Yankee, she defied her family and fled North. Dr Baer's mother was an unusually self-reliant, strong-willed, ambitious woman who, in spite of many difficulties, reared a large family and carved out an independent and success-

† Read at the meeting of the College, May 3, 1939.

* The writer wishes to acknowledge with thanks and grateful appreciation, data that have been supplied to him by Dr Baer's brother, Mr William G. Baer.

ful career of her own. There are many members of this College who recall with pleasure Mrs. Baer, in those days when she was associated with the late Dr Francis X. Dercum, as the owner and manager of his private hospital. Dr Baer cherished great respect and deep affection for his parents, who furnished him a background as well as ideals that did much to mould his character and to contribute to his success in later life.

His early schooling was in the public schools of Philadelphia. Even as a boy he was passionately fond of reading, yet language and literary courses were always difficult for him, whereas, he was naturally inclined to mathematics and the sciences. An anecdote of his school days is of interest because it so well explains certain characteristics which were well recognized in Dr Baer by all who were associated with him during his professional career. In his second year of high school, he did progressively worse in his studies. So much so that he was informed by the school authorities that he would be dropped. To the surprise of his teachers and classmates alike, he promptly announced his intentions of entering the University of Pennsylvania the following autumn. During that summer he worked with prodigious industry and triumphantly passed his college entrance examinationa admitting him to the Biological School of the University of Pennsylvania. His sensational entry into the University of Pennsylvania after failing in the sophomore year at the high school was nothing short of miraculous. The true story of how it came to pass was casually revealed by Frank Baer many years later when he admitted that he purposely flunked out of the high school because he dreaded the ordeal of making the speeches before the assembled school that were required periodically of the junior and senior students and made the supreme effort to enter college where he knew speech making could be avoided. Thus, in his school days he revealed the shyness which he never mastered and the dread of any form of public speaking that restrained him throughout his life. It is the explanation of why a man who was pre-eminent in his specialty consistently refrained from contributing to medical literature and steadfastly avoided speaking at medical and other public gatherings.

Baer found the Biological School to his liking; here he came under the influence of such stimulating teachers as Conklin and Macfarland and developed his love for the scientific method of approach. In 1900 he received his B.S. from the University of Pennsylvania and entered the Medical School of that institution, from which he was graduated three years later. Although he was obviously interested in studying medicine, nevertheless, during his years in the medical school he exhibited a restless desire to give up his studies and to gratify his constant urge for activity by entering upon some gainful occupation. His mechanical bent was well illustrated by the fact that, during vacations, he frequently worked on electrical construction projects. The tactful insistence of his father and the determination of his mother were no small factors in inducing him to finish his medical studies. Although apparently an indifferent student, who was rather bored by questions of purely academic interest, it was evident at examination time that his medical education was by no means superficial.

All through his boyhood and school life, Frank Baer was in more or less contact with medicine and hospitals by reason of his father's activities in the old Philadelphia Polyclinic Hospital. After graduation, he often acted as anesthetist or assistant for his father but, in spite of the opportunities that were offered, he never showed any interest in gynecology. Although he boasted that he had never attended a single lecture in ophthalmology during his medical course, he became fascinated with the subject through reading Dr George E. de Schweinitz's classic text, *Diseases of the Eye*. He evidently studied this book to good purpose, since it is said that he passed such an unusually fine examination in ophthalmology that it was a matter of favorable comment on the part of his examiner, Dr de Schweinitz. When this became known to Baer, he promptly decided to enter this field of medicine. His determination, optimism and courage are well illustrated by the fact that he had the temerity, without enjoying any experience as an interne in a hospital, to at once enter upon the exclusive practice of ophthalmology. For the next few years, until he had established himself in that specialty,

it may truly be said that he rarely left his office for fear of missing an opportunity to practice. He eschewed all forms of diversion and applied himself with extraordinary singleness of purpose to his work.

Shortly after graduation he became associated with Dr George E. de Schweinitz, that internationally famous figure in ophthalmology and former distinguished and beloved President of this College. This association was destined to persist for the next thirty-five years, until in August, 1938, Dr de Schweinitz died, only a few months before his devoted assistant. As years went on, this association with Dr de Schweinitz ripened into a deep and abiding friendship. There can be no doubt that the incomparable de Schweinitz furnished an inspiration and example to Frank Baer which had a profound effect upon his professional and intellectual development. He became one of Dr de Schweinitz's office assistants, a position which he filled with ever increasing skill and unfailing loyalty for over twenty years. Here he had the opportunity to work daily, shoulder to shoulder, with the greatest ophthalmologist of his generation. Baer was quick to appreciate what this opportunity meant and to learn valuable lessons from the skill and vast experience of his scholarly mentor.

Dr Baer's practical education in ophthalmology began when, shortly after graduation, he became a member of the Staff of the Eye Dispensary of the University Hospital. He later became Associate in Ophthalmology at the University of Pennsylvania and, in various capacities, served continuously on the Eye Service of the University Hospital from 1904 until the retirement of his chief in 1924. At this time his activities which had centered around the University Hospital were shifted to the Wills Eye Hospital, where he became Attending Surgeon, a position which he held up to the time of his death. In 1924 he was appointed Associate Professor of Ophthalmology in the Graduate School of the University of Pennsylvania.

For many years, Dr Baer's days were divided between his own office and that of Dr de Schweinitz, in the morning, and his work in the Dispensary or ophthalmological operating rooms in the afternoon. His days were full of intense activity that gave him

little time for leisure or diversion. He acquired outstanding skill in the various aspects of ophthalmology, but his greatest reputation was made in the surgery of the eye. In the performance of certain operations he attained a reputation that was national in scope. The confidence which Dr de Schweinitz placed in Dr Baer as an operating ophthalmologist is best born out by the fact that when Dr de Schweinitz found that he was suffering from glaucoma he turned to his able pupil with implicit trust and confidence for the operation which both knew was inevitable. Although it has been said that Baer was reluctant to contribute to ophthalmological literature and used every means to avoid appearing in public, in spite of the repeated persuasions of his beloved chief, he had a keen appreciation of the value of scientific research, was a constant student of his specialty and an unusually clear, incisive and popular teacher. He had no trepidation when it came to appearing before small groups of students. His dominating interest, however, lay in the practice of ophthalmology rather than in its academic aspects. In the early days of his practice, he not only conducted his Philadelphia office, but for a time also maintained an office in Wilmington, Delaware. Later on, in connection with his classmate, Dr Charles Mevay, he went daily to Atlantic City, where he also developed an extensive practice. As his own work in Philadelphia, and that with Dr de Schweinitz, became more and more exacting, he had to abandon these arduous and time consuming out-of-town activities.

In 1917 Dr Bear married Miss Beatrice Stephens of Wilkes-Barre, Pa. Shortly thereafter the United States entered the World War and Dr Baer left his bride of a few months and his active practice to enter the Army as a Captain in the Medical Corps. He went overseas as the Ophthalmologist to Base Hospital #20, an organization which was recruited from the University of Pennsylvania. In this group he found many of his oldest friends and closest associates, such as the late Drs J. B. Carnett and Floyd E. Keene, Dr Eldridge L. Eliason, who was perhaps his closest friend and confidant, as well as Drs George M. Laws, John Musser, Joseph Birdsall, George Outer-

bridge, who for years lived in his home, and numerous others, including the writer of this memoir. In the Army, as might be expected, his ability as an ophthalmologist soon attracted attention. He skilfully conducted the extensive Eye Service in Base Hospital #20 at Chatel-Guyon, France. In addition to this he was frequently sent to the front on operating teams. It was on one of these tours of duty that he contracted "flu," as a result of which he was returned to the United States in February, 1919, having been promoted to the rank of Major. It is of interest to note that while Dr Baer was convalescing from influenza in Paris, his first child was born at Philadelphia in the midst of the enthusiasm and rejoicing of Armistice Day.

After the war Frank Baer entered upon the happiest, the busiest and the most successful years of his life, during which he attained the prime of his intellectual and professional successes. During his last twenty years he continued to exhibit the same close application to his practice which had marked the earlier period of his career. He was essentially a skilled practitioner of ophthalmology and a brilliant operator. During the latter years of Dr de Schweinitz's life, it was Dr Baer who assumed a large part of the burden of his chief's practice and did practically all of his operating. He carried on these added duties with cheerful efficiency in addition to his own ever increasing practice. Baer throve on activity. He seemed to enjoy living under a nervous tension and delighted in those tasks which called for agility, speed and nicety of judgement. It required an extraordinary degree of energy, day after day, to accomplish the tremendous task which he set for himself. Although he steadfastly refused to lessen his pace, in spite of the pleadings of his family and friends, as he grew older, the tension began to tell upon his health, which gradually failed, until he succumbed to a broncho-pneumonia in a final illness which lasted scarcely a week. He is survived by his widow and five children.

He found his chief diversion in associations with his family, to whom he was passionately devoted. When he acquired his beautiful country home in Ardmore he fulfilled one of the great ambitions of his life. Here he spent every available moment,

delighting in his children in whom, with justice, he took the greatest pride. Aside from this enjoyment of his family, his other recreations consisted in bridge, which appealed to his analytical mind, and golf.

Dr Baer became a Fellow of this College in 1910. He was also a member of the American Ophthalmological Society as well as the American Medical Association and his local county and state societies.

Frank Baer had many friends to whom he was intensely loyal and by whom he was much beloved because of his uncompromising honesty, his forthrightness, his innate warmth of heart and his never failing sense of humor. His devotion to his patients was outstanding. He had a high sense of duty and firmly believed that his first responsibility was to those who entrusted themselves to his professional care. He made their problems his own. To every patient he unfailingly gave the best that was in him. Like his distinguished preceptor, he was as deeply interested in and showed as much personal concern for the poorest and the most troublesome ward case as he did for those who were in more fortunate circumstances. His invariable rule was to inspire his patients with hope and courage.

He occupied a unique position among the ophthalmologists of this country. It will be difficult to find anyone to adequately take his place. His loss is deeply felt by the many who were his patients, his friends or his colleagues, but sorrow at his death is particularly keen among the Fellows of The College of Physicians of Philadelphia, so many of whom will ever count it a privilege to have been numbered among his oldest and closest friends.

College Notes

Elected to Fellowship (May 3, 1939):

H. D. Barnshaw, Raymond W. Brust, Glen Gregory Gibson, Patrick Boland Hughes, Norman Merle Macneill, D. Sergeant Pepper, Norman Price Shumway, George Willauer.

Necrology:

Edward H. Goodman (non-resident Fellow). March 6, 1939.
Alfred Stengel. April 10, 1939.
Henry M. Fisher. April 27, 1939.
Ellis E. W. Given. May 11, 1939.
George M. Boyd. May 20, 1939.
Henry K. Pancoast. May 20, 1939.

Resolutions of a Public Character Passed by the Council:

1. The College of Physicians of Philadelphia and its Section on Ophthalmology wish to express their objections to the passage of House Bill No. 716, which would permit optometrists to issue certificates of ocular and visual efficiency required by the laws of the Commonwealth:

To make the examination which is necessary to obtain the facts justifying such certificate, a thorough medical training is needed, and optometrists do not have such qualifications. Therefore we feel that the passage of House Bill No. 716 would jeopardize the whole reason for such examination and the granting of such certificates.

Were the applicants for the Blind Pension Fund to be so examined, the Fund would be placed in danger, since the examination is a most complete ophthalmological one and can be properly made only by a well trained ophthalmologist.

Certain diseases affect the peripheral portion of the visual area long before the central portion is involved and only examination by a well trained physician will discover these cases.

The State medical offices are using the reports on the conditions of several of these groups as a basis for statistical information, and such information, unless supplied by those sufficiently trained, will be worthless for such a purpose. *April 25, 1939.*

2. The College of Physicians of Philadelphia endorses the plan now under consideration for a health center at the Glenwood Cemetery plot in North Philadelphia. *May 23, 1939.*

The Fellows

W. Osler Abbott addressed the New York Roentgen Society at the New York Academy of Medicine, December 19, 1938.

Leighton F. Appleman is now consulting surgeon, Wills Hospital.

Francis J. Braceland has been appointed assistant professor of psychiatry, Graduate School of Medicine, University of Pennsylvania.

Williams B. Cadwalader was elected president of the American Neurological Association, May, 1938.

Garfield G. Duncan was appointed associate professor of medicine at Jefferson Medical College, April 20, 1939, and in the same month was elected to fellowship in the American College of Physicians.

A. Bruce Gill received a D. Sc. degree, *honoris causa*, from Muskingum College, 1938, and delivered a Sir Robert Jones Lecture at the Hospital for Joint Diseases, New York City, February 23, 1939.

Donald Guthrie, Non-resident Fellow, of Sayre, Pa., was last year elected a member of the Royal Hungarian Medical Society, and on February 9, 1939, read a paper before the Harvard Medical School.

A. Parker Hitchins has been appointed first George S. Pepper professor of public health and preventive medicine at the University of Pennsylvania.

Chevalier Jackson delivered the Packard Lecture for 1939 at the meeting of the Philadelphia Pediatric Society on April 11, 1939.

Harold R. Keeler was elected to fellowship in the American College of Physicians in December, 1938.

A. Graeme Mitchell, Non-resident Fellow, of Cincinnati, addressed the Philadelphia Pediatric Society on March 14, 1939.

Charles F. Nassau was appointed director of the Department of Public Health of Philadelphia, January 14, 1939.

Charles C. Norris has been appointed (March, 1939) special consultant, U. S. Public Health Service, Division of Venereal Diseases, Philadelphia.

Eugene P. Pendergrass addressed the South Carolina X-ray Society, April 12, 1939; the State Medical Association of Texas, May 9, 10, 11, 1939; the Mahoning County Medical Society, Youngstown, Ohio, April 20, 1939.

George E. Pfahler is an honorary vice-president of the third International congress of scientific and social campaign against cancer, scheduled to be held at Atlantic City, September 11–16, 1939.

I. S. Ravdin delivered two lectures, February 6 and 7, 1939, before the New Orleans Graduate Medical Assembly.

Lauren H. Smith became, December 1, 1938, physician-in-chief and administrator of the Institute for Mental Hygiene and the Department for Mental and Nervous Diseases of the Pennsylvania Hospital.

Joseph Stokes, Jr., succeeds John C. Gittings, on the latter's retirement, as William H. Bennett professor of pediatrics, School of Medicine, University of Pennsylvania.

William D. Stroud, elected president of the American Heart Association, February, 1939, spoke at the New York Academy of Medicine, December, 1938, and before the Chicago Heart Association, January 31, 1939.

L. M. Tocantins lectured before the University of Toronto Faculty of Medicine, December 11, 1938.

Norris W. Vaux spoke before the Medical Society of the County of Kings (Brooklyn, N. Y.), December 20, 1938; the Mid-South Medical Assembly, at Memphis, Tennessee, February 14, 1939; and in Norfolk, Virginia, March 27, 1939.

The Library

RECENT ACQUISITIONS OF HISTORICAL INTEREST

Gilbertus Anglicus. *Compendium medicinae.* Lyons, 1510. This is the first edition of one of the fundamental medieval textbooks of medicine; it comes to the library late, but all the more welcome on that account. A number of Fellows and others aided the library in its purchase.

De Renzi, Salvatore. *Storia della medicina Italiana.* 5 vols. Naples, 1845–8. Happily, we need no longer apologize for the absence of this classic history of Italian medicine from our collection of secondary historical sources.

Fantozzi, P. P. *Certamen medico iuridicum coram Apolline praehibitum.* Venice, 1680. Sent to us from Italy, along with the Vandelli immediately below, as the gift of Professor Dean P. Lockwood, of Haverford College.

Vandelli, Domenico. *Dissertatio de arbore draconis.* Lisbon, 1768. This little treatise, by one of the vigorous opponents of von Haller's irritability theory, is dedicated to Walter Wade, the Irish botanist and physician.

[Bosquillon, Edouard François Marie]. *Catalogue des livres rares et précieux de feu M. Bosquillon.* Paris, 1815. Bosquillon was a physician of the Hôtel-Dieu, edited Hippocrates, and translated Cullen into French. Gift of Samuel X. Radbill, M.D.

An account of the rise, progress, and termination, of the malignant fever, lately prevalent in Philadelphia. Phila., Johnson, 1793. This anonymous pamphlet seems to be based largely on William Currie's "Description" (below), published a few months earlier, and referring obviously to Rush (though discreetly not mentioning him by name) and his theory of the origin of the fever, says: ". . . but the majority of his fellow citizens think that he has carried the spirit of discovery too far in tracing its origin." Gift of Samuel X. Radbill, M.D.

Currie, William. *A description of the malignant, infectious fever prevailing at present in Philadelphia. . . .* Phila., Dobson, 1793. One of the earliest of the yellow fever pamphlets, and one which, strangely enough, considering Currie's connection with this College, was not listed in our catalogue.

Smith, Hugh. *The female monitor, consisting of a series of letters to married women. . . .* Wilmington, 1801. Earlier American editions of this work had appeared in Philadelphia; this edition is of special interest in that it was edited

by John Vaughan, one of Wilmington's leading physicians, who added to it a treatise of his own (so to speak) on diseases of infants – certainly, one of the earliest American works on this subject. Gift of Thomas R. Neilson, M.D.

The pocket Aesculapius; or, every man his own physician. Edinburgh, 1806. The biologic strains of these natural sons of Aesculapius are so indeterminate that it is difficult to trace their individual family trees. The present "author" claims to have acquired some of his most valuable receipts during his residence among the Indian tribes. Gift of Isaac Starr, M.D.

[U. S.] 20th Congress, 1st session. Doc. No. 66. Ho. of Reps. Joseph G. Nancrede. *Memorial of Joseph G. Nancrede, vaccine physician, Philadelphia.* January 14, 1828. Read, and laid upon the table. Washington, Gales & Seaton, 1828. In this memorial Dr. Nancrede, the Philadelphia physician of French descent, pleads with the Congress to establish a vaccine institute at Philadelphia, where the memorialist has been entrusted, as he says, since the year 1816 with the public vaccination of the city. A national vaccine institute had been established at Baltimore in 1813, but that agency was annulled in 1822, owing to an unfortunate error that occurred in the institution. Dr. Nancrede had reason to believe that the Congress would consider establishing a new national institute at Philadelphia, in view of the epidemic of small pox then raging throughout the country, and in view of the city's medical eminence. "Read, and laid upon the table." Gift of Edward B. Krumbhaar, M.D.

MANUSCRIPTS

Hospital and Dispensary for the Relief of Diseases of the Rectum and Genito-Urinary Organs. 2 vols.: minute-book; account-book. Philadelphia, 1875–1886. Primary sources for a bit of local medical history that has never been written. Gift of Mrs. Howard W. Lewis, through Francis R. Packard, M.D.

Letter of A. F. Chomel, the French clinician, dated June 4, 1833, agreeing to visit the sister of Mme Minette (to whom the letter is addressed), but only on condition that her regular physician be present also! Gift of Edward B. Krumbhaar, M.D.

Financial report of the Pennsylvania Hospital for the year 1812. Accompanying the original manuscript is a copy of the printed version. Gift of E. Olivia White, M.D., through William Egbert Robertson, M.D.

Letter and photograph sent to Dr. William F. Norris by a grateful Civil War veteran on whom Dr. Norris had operated 20 years earlier (1863). Gift of George W. Norris, M.D.

Note and bill sent (on her request) by Philip Syng Physick to his patient, Miss Butler, a close connection of Pierce Butler, the South Carolina statesman. Gift of William Drayton, Jr., M.D.

Small legal document concerning one James Sutton, barber-surgeon, of Whitechapel, dated the 17th year of King James' reign in England [i.e., 1619–20]. Gift of Edward B. Krumbhaar, M.D.

Two lots of ships' Bills of Health, port of Philadelphia, 1890–1930. Gift of Samuel X. Radbill, M.D.

Copy of the privately printed "Oath of Hippocrates" annually presented by Dr. William J. Kerr, of San Francisco, to his students upon their graduation. Gift of William J. Kerr, M.D., through O. H. P. Pepper, M.D.

The library has been fortunate in receiving within recent months two exceptionally fine collections of books on special subjects. One is the ophthalmological library of the late Dr. George E. de Schweinitz, a former president of the College. The other is the library of another Fellow, the late Dr. Lawrence F. Flick, American pioneer in the field of tuberculosis-prevention. Dr. Flick had willed to the library his remarkable collection of pamphlets on tuberculosis, contained in some 180 large, bound volumes, with an index to them; through the generosity of Dr. Flick's son, Dr. John B. Flick, the rest of the library has been added to the original bequest.

The memory of two Fellows of the College who have recently died has been honored in a particularly felicitous way. Several friends and associates of Dr. Floyd E. Keene and Dr. Alfred Stengel have sent to the library cheques to the amount they would have expended on flowers, with the request that these be devoted to the purchase of books.

The Mütter Museum

The collections of the Mütter Museum are now being rearranged in such a manner as to bring related objects together. An arrangement of the dry and wet specimens by diseases has been begun; all of the specimens showing arthritis, for example, that were once scattered throughout the Museum, have now been brought together, and all kinds of material pertaining to syphilis and tuberculosis have been similarly treated. The extensive collection of fractures has been re-assembled according to anatomical relationships. The collection of deformed pelves is now in a lighter case and so placed that the specimens can be studied more easily. The Matthew H. Cryer collection of facial and maxillary specimens and the Cryer comparative anatomy collection have been enriched by the addition of similar material from other parts of the Museum, and the latter collection has been arranged in phylogenetic order.

RECENT ACQUISITIONS

Plaster cast of the left hand of a 232 cm. giant of the infantilism type. Gift of Charles D. Humberd, M.D.

Stethoscope formerly belonging to John Wilson Johnson, M.D. Gift of A. C. Morgan, M.D.

The Committee on College Collections

RECENT ACQUISITIONS

Bronze medal of Joseph Leidy, made for the American Association of Anatomists by R. Tait McKenzie, M.D., 1938. Gift of W. H. F. Addison, M.D.

Oil portrait of Jacob Solis-Cohen, M.D. Painted by W. T. Thomson. Gift of the College's Section on Otolaryngology. (Cadwalader Hall)

Microscopic preparations on pathology of the eye, prepared by Josef Hyrtl. Gift of Simon S. Leopold, M.D.

Framed photograph of John H. Girvin, M.D. Gift of Miss Helene Girvin, through Francis R. Packard, M.D. (Office of the College)

Bronze medal, made for the Unio internationalis contra cancrum in commemoration of the 40th anniversary of the discovery of radium by Pierre and Marie Curie, 1898–1938. Gift of Edward B. Krumbhaar, M.D.

Cholera Hospitals. Framed copy ($32\frac{3}{4}'' \times 22\frac{3}{4}''$) of an address presented by the physicians-in-chief of the Philadelphia cholera hospitals to the Select Council, Monday, August 6, 1832, and by the latter referred to the Sanitary Committee with the recommendation that it be published. This is the published address. The peak of the epidemic in Philadelphia was reached on August 6 (J. S. Chambers, *The conquest of cholera*, New York, Macmillan, 1938, p. 72), when 176 new cases and 71 deaths were reported. An astonishing display of hostility toward the physicians of the cholera hospitals led them to make this explanation of their position with a request for protection. In the College library, incidentally, are the cholera-hospital case-books kept by two of these physicians, Joseph Parrish and Samuel Jackson. This interesting new document is the gift of Mrs. Melvin M. Franklin, carrying out the wish of her husband, the late Dr. Franklin.

Bronze medal, made in commemoration of the 50th anniversary of the institution of the Johns Hopkins Hospital, 1889 1939. Two copies, the gift of O. H. P. Pepper, M.D.

The Surgical Approach to Diseases of the Heart*†

By Claude S. Beck, M.D.

The title of this presentation implies that there exists a surgical approach to diseases of the heart. I wonder whether the surgical achievements on the heart should be so dignified by this term. Only a small proportion of the patients suffering from heart disease are treated by operation. Practically all cardiac lesions are treated by nonsurgical methods. Perhaps we entertain something of a hope that other, more effective methods of treating diseases of the heart will be discovered, and this even though the cardiac invalid must be subjected to an operation. If you grant the existence of a surgical approach to diseases of the heart or if you entertain the hope that there might be such a thing, perhaps I shall be permitted to make a few remarks.

The surgical approach to diseases of the heart has its greatest opportunity for accomplishment in the research laboratory. In the laboratory ideas can be tested and those that have practical value can be applied to human patients. I have in mind the work on defibrillation of the ventricles. Experimentation has yielded an effective method which can be applied to human patients. I have every confidence that life will be saved by application of a method worked out in the experimental laboratory for defibrillation of the ventricles. What has the surgical approach to offer in sclerosis of the coronary arteries? We can say that the surgical approach commits itself to study all procedures that might give the heart what it needs, namely, more

* Mary Scott Newbold Lecture XLIII, The College of Physicians of Philadelphia, April 5, 1939.

† From the Department of Surgery, Western Reserve University School of Medicine and the University Hospitals, Cleveland, Ohio. Aided by a Grant from the Josiah Macy, Jr. Foundation.

oxygenated blood. To be investigated, then, are vascularized grafts, intercoronary communications and factors that will make them patent, stasis in the coronary venous system, ablation of sympathetic nerves and perhaps other procedures that may suggest themselves in the future. What of benefit will come from such studies remains to be seen. The surgical approach to the heart for this present day and age is closely related to the experimental laboratory. My presentation is based upon animal experiments.

THE CIRCULATION IN THE CORONARY ARTERIES

Vascularized Grafts on the Surface of the Heart. The heart is anchored in the body by the structures at its base. The structures at the base of the heart furnish the only continuity between the heart and the rest of the body. In the fat at the base of the heart are small arteries which connect with the coronary arteries. These anastomoses were demonstrated by the injection of India ink into the coronary arteries. The injection mass could be traced into the mediastinal structures (1). Under normal conditions, these anastomoses are small and it is doubtful whether they carry any significant quantity of blood. However, after the coronary arteries have been occluded by placing silver bands around the arteries, these anastomoses increase in size and number (2). It has been shown also that adhesions to the heart contain blood vessels that connect with the coronary arteries. India ink injected into the coronary arteries was traced through the adhesions into the pericardium, diaphragm and chest wall. These injection studies were carried out on human hearts that had adhesions from rheumatic heart disease (3).

In view of these facts, we can raise the question as to whether the anatomical arrangement of heart and pericardium is advantageous or otherwise in the presence of coronary artery disease. Is the heart deprived of a collateral vascular bed because it has so little continuity with the adjacent tissues? The answer to this question is of considerable importance in that it will determine whether or not a plastic operation would be beneficial for patients with coronary artery disease. The author was the

first to carry out experimental studies on this subject. They were begun toward the close of 1931 and have been continued to the present time (4) (5).

The tissues that are available for grafting upon the heart are parietal pericardium, mediastinal fat, skeletal muscle and omentum brought up through an opening in the diaphragm. A few experiments were done in which spleen and stomach were grafted upon the heart. We believe that better anastomoses developed in the experiments in which some degree of obstruction to the coronary arteries was also provided. The production of coronary artery occlusion became a problem in itself. In the early experiments, the arteries were taken down in abrupt steps in successive operations by squeezing together a silver band placed around each of the coronary arteries. Later on a special screw clamp was devised for this purpose by my associates, Dr. Frederick Mautz and Dr. John Thornton (6). This clamp could be placed around a coronary artery and could be tightened at successive operations. More recently my assistant, Dr. Kenton Phelps, devised a clamp which utilizes the principle of osmosis (7). This clamp when placed around an artery gradually occludes the artery. Complete obstruction of an artery can be produced without reoperation and the rate of closure can be made as rapid or as slow as desired. This ingenious clamp should be of great help in this work because it produces gradual and progressive obstruction and in these respects the occlusion is similar to that in man.

The order of procedure carried out in our early experiments was to dissect out the two major branches of the left coronary artery and the right coronary artery and to place silver bands around these arteries. The arteries were slightly constricted. The epicardium was then removed from the heart by mechanical means and grafts were placed upon the denuded myocardium. Repeated operations were carried out for the purpose of increasing the obstruction to the coronary arteries. In this way we were able to produce occlusion of the right coronary, the circumflex branch of the left coronary artery and also the descending ramus of the left coronary artery. The septal branch

was not occluded. These experiments carried a high mortality. If one artery was constricted too much at any one step, ventricular fibrillation appeared and terminated the experiment. We were able to produce almost complete closure of all coronary arteries with survival. The specimens were injected in one of two ways. One injection method was through the coronary arteries, the injection mass going out into the grafts. The other method was through the grafts into the coronary bed. The cleared specimens showed vascular anastomoses between the coronary arteries and the arteries of the grafts.

We must remember that this is an anatomical and not a physiological demonstration. We do not know how much blood goes through these channels. Indeed, we do not know the direction of the flow, whether it is into or away from the heart.

Another point brought out by the experiments, and one that I believe is important, concerns the distribution of blood to various parts of the myocardium. If a relatively small area of the left ventricle is made ischemic, the normal co-ordinated ventricular contraction is replaced by fibrillation. This can be demonstrated by placing ligatures around four or five branches of the arteries that converge toward one area of the ventricular wall. Ventricular fibrillation was produced in 24 successive experiments in which the area of anoxemia measured 3 to 4 cm. in diameter. In contrast with these experiments showing the fatal results of localized anoxemia, we have shown that if the anoxemia is uniform throughout the entire heart it seems that considerable constriction can be applied to the coronary arteries without producing ventricular fibrillation. On the basis of our experiments it would seem that the right and left coronary arteries could be constricted at their origins from the aorta about one third of the cross section, with recovery. In this second type of experiment, which resulted in recovery, the total coronary blood flow was probably reduced to a greater extent than in the first type of experiment, which did not result in recovery. The effect of anoxemia as stated by Wiggers is as follows: "Anoxemia of the ordinary heart muscle either increases the irritability of foci in the ventricular muscle or causes delayed conductions and

regional blocks which permit re-entry of excitation waves into normal areas. Either of these factors would explain the frequent premature ventricular contractions, tachysystolic rhythm or fibrillation." We can readily understand that the communications between the peripheral branches of the coronary arteries become increasingly important as sclerosis develops in the major coronary arteries. Under normal conditions the coronary arteries are practically end-arteries. If the descending ramus of the left coronary artery is cut, only a few drops of blood per minute flow from the distal end of the vessel. As sclerosis of the major coronary arteries appears intercoronary communications develop. In some patients it would appear that these communications develop freely and the heart makes a good response to the occlusion of an artery. In others the response is less favorable. In the experimental work we were able to occlude a major coronary artery without producing an infarct and this was made possible by the development of intercoronary communications. For example, if the descending ramus was completely taken down in two or three operative steps, anastomoses developed with the circumflex ramus and the right coronary artery, so that the muscle mass normally supplied by the occluded artery was never sufficiently anoxemic to undergo fibrosis. We do not know what the factors are that determine the origin and growth of an artery. Perhaps one factor is a pressure differential, i.e., a relatively low arterial pressure in the area formerly supplied by the occluded artery compared with the higher pressure existing in the other areas of the heart. Perhaps metabolic factors also exist. We know that inflammation brings about an increase in arterioles. Whatever the factors are, it would seem that the intercoronary communications do not develop to the same extent in all patients with coronary sclerosis.

The distribution of blood in the ventricular musculature appears to be of considerable importance. This aspect of the coronary artery problem is quite distinct from that of increasing the blood supply through vascularized grafts. Any operative procedure that improved the peripheral distribution of the blood passing through the major coronary arteries, even though these

arteries are sclerotic, would have possibilities of a beneficial nature. We have not carried out comparative studies to determine whether or not our operation brings about an improved peripheral distribution of blood in the presence of, let us say, one occluded and two patent arteries. It is possible that the inflammatory reaction on the surface of the heart following removal of the epicardium does open up intercoronary communications. Perhaps the presence of a graft on the ventricles might have some effect in this direction. It may be that this factor, if it actually exists, explains the early improvement that we have encountered in our patients after operation. This early improvement cannot be explained on the basis of additional blood from the grafts, because it is too early for extracoronary communications to develop.

Dr. Harold Feil selected 30 patients with coronary sclerosis and angina pectoris for operation. We desired to determine from this group of patients whether or not vascularized grafts placed upon the heart were of any benefit in this disease. I shall not discuss the selection of patients for operation, the operative procedure or the mortality. These are not of great importance to the subject at its present stage of development. The important problem is what intercoronary and what extracoronary communications can be produced by operative methods. Information on this subject will be obtained from clinical results after operation and from the injected specimens after death.

Briefly stated, I believe that I can say that the clinical result after operation has been one of improvement. In so far as anyone can tell by clinical measurements, some of the patients were definitely improved. Dr. Feil has made these measurements and his conclusion is that the operation has contributed to improvement (8). I shall not discuss the clinical result further. As you know, this subject contains many variable factors and the careful judgment of an experienced clinician is necessary, to make the appraisal of the results, if the appraisal is to be of value. Up to the present time, three patients have died who survived the operation and who went along over a sufficient period of months for collateral vessels to develop. One of these had the

least clinical improvement of the group. He weighed 87 pounds when he died. The grafts were atrophic and no injection mass entered the grafts. The second belonged to the second group of clinical results and a few anastomoses were demonstrated. The third had a good clinical result. The injection mass was placed in the coronary arteries through the aortic ostia. It passed out into the grafts and dripped from several points in the grafted tissues. The injection mass was a solution of barium and was thicker than blood. Barium could be seen in the vessels of the grafts.

In conclusion, I can say that we have demonstrated anatomical vascular anastomoses between grafts and the heart in the human patient suffering from coronary artery disease. This demonstration is to be looked upon as a principle in surgery. We cannot say that this principle of producing anastomoses between small blood vessels will find application in treating patients with coronary artery disease. The amount of blood going through the anastomoses might not be sufficient to justify the operation. The best method for producing blood vessels must be brought to light. I think my attitude is conservative when I say that we have produced vascular anastomoses between the coronary arteries and the arteries of tissues grafted upon the heart. We have not demonstrated that these anastomoses are rich enough and large enough to carry an appreciable quantity of blood. Additional data on this subject will be obtained by the study of injected specimens from patients who have had the operation.

Venous Stasis in the Coronary Circulation. I should like to discuss the effect of stasis in the coronary circulation as produced by placing ligatures upon coronary veins. Ligation of a major vein with a major artery elsewhere in the circulatory tree has received considerable study. The results of these studies can be referred to only briefly. Both clinical and experimental observations support the conclusion that after a major artery to an extremity has been ligated the incidence of ischemic necrosis in the extremity is reduced by ligation also of the major vein. In experiments on rabbits, Brooks, Johnson and Kirtley (9) found that focal necrosis was reduced from 17 per cent, which

was observed after ligation of the artery alone, to 2 per cent, which was observed after both artery and vein were ligated. They observed massive necrosis to have occurred in 29 per cent after ligation of artery alone and in 2 per cent after ligation of the vein and artery. They also observed late ulceration in 7 per cent and 6 per cent of their experiments respectively. Curiously enough the ulceration that occurred late was observed in about equal frequency in each series of experiments, so that it would appear that the beneficial effect of venous ligation did not persist indefinitely but disappeared after a period of time. Edwards and Holman (10) noted an increase in the amount of blood that came from the distal stump of the ligated artery after the corresponding vein was ligated and concluded that the blood flow in the distal part of the extremity was increased by the ligation of the vein. Brooks and his coworkers, however, noted a reduction in temperature of the limb after ligation of the artery. They noted also a further reduction in temperature after ligation of vein was added to ligation of artery and concluded that ligation of vein brought about in the limb a reduction in the blood flow peripheral to the ligature. According to this conclusion the beneficial effect of venous ligation in producing a reduction in the incidence of early necrosis of tissues takes place in the presence of a reduction in blood flow. It should be stated that after the artery has been ligated the pressure in the peripheral arterial tree is increased by ligation of vein. Also the pressure in the venous system peripherally is elevated by this procedure.

Similar studies on the veins and arteries of the heart were carried out by Gross, Blum and Silverman (11). They ligated or occluded by other methods the coronary sinus and found that occlusion of this large venous channel where it entered the right atrium carried a mortality of 42 per cent occurring in the first 24 hours after the occlusion of the vein. They carried out a series of experiments in which ligation of the descending ramus of the left coronary artery was done at a point 2 cm. from the ostium of the circumflex artery. The mortality in these experiments was 53 per cent occurring within 24 hours after the occlusion was produced. In another series of experiments occlusion

of the coronary sinus was added to this experiment. The mortality in these experiments with occlusion of both artery and vein was 55 per cent within 24 hours after the occlusions were produced. They concluded that complete ligation of the coronary sinus did not reduce mortality after ligation of the coronary artery. They measured the size of the infarcts in each series of experiments and concluded that the size of the infarct was definitely smaller in those experiments in which the vein was also ligated. These authors hoped to apply this procedure to the human heart in order to increase the vascular tree.

Gregg and Dewald (12) (13) carried out physiological studies after ligations of coronary vessels. They found that the amount of blood flowing through the left coronary artery was considerably reduced after ligation of the coronary sinus. They ligated the left coronary artery and the coronary sinus and found that the systolic pressure in the artery peripheral to the ligature was approximately equal to or even higher than aortic systolic pressure. They concluded that this pressure had its source largely in other nonoccluded arteries. After occlusion of the coronary sinus the systolic pressure in the sinus approached or exceeded systolic pressure in the aorta. The retrograde blood flow was markedly elevated from the descending ramus of the left coronary artery after the coronary sinus was ligated. When this artery was ligated and cut, the retrograde flow was about 1 cc. per minute. After ligation of the coronary sinus the retrograde flow from the artery was as high as 39 cc. per minute. The blood was highly unsaturated, containing only 3 to 4 volumes per cent of oxygen. Gregg and Dewald do not believe venous ligation is a method of "choice" for encouraging the blood supply to a potentially infarcted area of the myocardium. Thornton and Gregg (14) studied the problem after the coronary sinus had been occluded 30 days. They found that the measurements obtained by Gregg and Dewald had practically returned to normal levels. It would appear, then, that the alterations in the circulation produced by occlusion of the coronary sinus are transient in their duration. It is of interest to note that Brooks found the incidence of late necrosis in the leg unaffected by venous ligation.

Fauteux, of Montreal, ligated the magna cordis vein and the descending ramus of the left coronary artery. He concluded from his experiments (unpublished) that ligation of this vein reduced the mortality that follows ligation of the artery alone. Fauteux was eager to ligate this vein in patients with sclerosis of the descending ramus of the left coronary artery and recently carried out this operation.

Additional Experiments on Ligation of Coronary Artery and Vein

Dr. A. E. Mako and I carried out experiments on this subject. We desired to answer two questions: (1) whether ligation of coronary veins reduced mortality after ligation of an artery; and (2) whether ligation of veins brought about a reduction in the size of the infarct. The artery that we selected for our studies was the descending ramus of the left coronary artery just below the bifurcation of this artery. The veins that we ligated were either the coronary sinus where the sinus entered the right atrium or the magna cordis vein where it lay beneath the left auricle. In some of our experiments we ligated also the veins from the right ventricle as they entered the right atrium, thus producing stasis in almost the entire venous system of the ventricles.

Ligation of Coronary Veins. The slowing of the heart rate and the cyanosis of the ventricles following ligation of coronary veins have been noted by others. The mortality following complete ligation of the coronary sinus in our hands was about 2 per cent. Gross, Blum and Silverman reported a much higher mortality, which I believe must be accounted for on the basis of technic, anesthesia and the avoidable complications to the operation.

Ligation of Coronary Artery. The left coronary artery was dissected at its bifurcation. The descending ramus was doubly ligated and cut immediately below its bifurcation. Every care was taken to avoid all factors that might increase the mortality rate. Three series of 10 dogs each were done. The mortality was 9, 8 and 7, a total of 24 in 30 or a mortality rate of 80 per cent. The 6 dogs that recovered were observed over a period of 12 days to 8 months.

Ligation of Coronary Vein and Artery. Four series of experiments were done. The results were as follows: Ligation of vein

with ligation of artery at same operation, 3 recovered, 7 died, recovery rate 30 per cent. Ligation of vein, one to two weeks later ligation of artery, 5 recovered, 5 died, recovery rate 50 per cent. Ligation of vein, six weeks later ligation of artery, 5 recovered, 5 died, recovery rate 50 per cent. Ligation of vein, four months later ligation of artery, 7 recovered, 10 died, recovery rate 41 per cent. The total mortality rate was 57 per cent.

Conclusion. In these experiments the mortality was reduced from 80 per cent when the artery alone was ligated to 57 per cent when ligation of vein was added to ligation of artery. A sufficiently large number of experiments was done to give some significance to these figures. It appears also that the beneficial effect of coronary vein ligation was least when vein and artery were ligated at the same operation, that it was greatest when the interval was 1 to 6 weeks, and that it became less after an interval of 4 months. It would appear that the beneficial effect upon mortality of vein ligation varies with the interval of time between the ligation of vein and the ligation of artery. In this respect the results are in accord with the observations of Brooks and of Thornton and Gregg.

We encountered difficulties in measuring the size of the infarcts in the heart. In no experiment did ligation of the vein prevent the formation of an infarct after ligation of the artery. Without presenting detailed measurements on this subject I believe I can say that the infarcts were slightly smaller in the group of vein and artery compared with the group of artery alone.

At the present time it is difficult to say whether or not ligation of coronary veins should be done on patients with coronary sclerosis. On the basis of our experiments the beneficial effect is not great but it is not entirely absent.

FIBRILLATION OF THE VENTRICLES AND CARDIAC STANDSTILL. THE ESTABLISHMENT OF A RESUSCITATION SQUAD IN HOSPITALS

When the pumping action of the heart ceases and the arterial pressure disappears, the ventricles either come to a complete standstill or go into incoördinate fibrillary twitchings for a while before every vestige of movement disappears. Both of

these mean death unless a co-ordinated contraction is restored to the heart. In the vast majority of cases attempts at restoration are futile. A myocardium poisoned by bacterial toxins or weakened by chronic disease cannot be made to function. A normal heart that suddenly stops can be made to beat again. I have in mind the sudden deaths that occur in our hospitals from sudden, unexpected stoppage of the heart. If failure occurs in the operating room, restoration should be possible in the following conditions—hemorrhage, inadequate cardiac filling from reduction of abdominal pressure, drug effects with transient action, such as those produced by ether, chloroform, nitrous oxide, intraspinal novocaine etc., medullary paralysis associated with brain operations, ventricular fibrillation from manipulations of the heart or from the use of the electric cautery, vagus inhibition from pulling on abdominal organs, cardiac trauma, pneumothorax, and asphyxia.

The requirements for restoration of life demand two different and distinct activities. One activity centers upon getting oxygen into the lungs, the other is to move oxygen from the lungs to the brain. Of all tissues the brain is the least viable. It dies in a few minutes from lack of oxygen. The period of anoxemia that can be tolerated by the brain is of short duration, probably from three to five minutes. After this period irreparable damage seems to occur. This factor determines success or failure in resuscitation. The period of cerebral anoxemia can be terminated ad libitum and it can be done in a few moments. The necessary steps are simple and not formidable. One consists in delivering oxygen into the lungs. We have a special apparatus for this in our laboratory and in our operating rooms. It delivers intermittently air or oxygen into the lungs either with a face mask or into an intratracheal tube. Aeration of the lungs must be perfectly adjusted. The Drinker respirator is not satisfactory for resuscitation because the heart cannot be massaged and an artificial circulation of blood cannot be produced. At the same time that oxygen is blown into the lungs the oxygenated blood is moved from the lungs by direct massage of the heart. An incision is made through the chest wall between the fourth and

fifth ribs. One or two cartilages are cut above and below so that the chest can be widely opened and the hand inserted. The pericardium is opened. The heart is grasped in the hand. If both ventricles cannot be compressed in the hand, effective emptying can be accomplished by compressing the heart against the chest wall with the hand beneath the heart. The emergency is now over. The pulse can be felt and a blood pressure of about 60 mm. of mercury is produced by manual massage. This can be considered the first stage in resuscitation. It must be instituted promptly. The operator and the anesthetist must know what they are going to do. Time cannot be taken to call for help.

While the first stage in resuscitation concerns the central nervous system, the second stage, which we now enter, concerns the heart. While the first stage must be done by the surgeon and by the anesthetist who are present when the emergency appears, the second step is done by someone who is trained for this work. Time is almost not a factor in the second stage. The heart, if it was normal before the emergency, can always be revived. If it is fibrillating, it must be defibrillated. If it is at a standstill, it must be made to beat. I believe the writer is the only one who has ever defibrillated the human ventricles. I have done this on two patients. The fibrillation was made to disappear and a normal co-ordinated beat was obtained. However, the first stage in each patient was unsatisfactory in that the nervous system was allowed to die. Respiration and reflexes never came back.

Defibrillation of the ventricles can now be done with surprising ease. I shall not go into the physiology of the subject except to mention the names of Prevost and Battelli (15), of Hooker (16) (17) and of Wiggers (18) (19). Mautz (20), working in our surgical laboratory, showed that procaine reduced the irritability of the heart, and the use of procaine became an important adjunct to defibrillation methods which, up to that time, were effective in only about half of our experiments. Large electrodes are placed upon the heart and a current of 1 to 1.5 amperes is sent through the heart. If the fibrillation does not stop, the

irritability of the myocardium is reduced by procaine. Two cubic centimeters of five per cent solution are injected into the right ventricular cavity and massaged around the heart into the coronary arteries. This drug reduces the tone of the myocardium and the heart usually becomes more flabby after its use. The current is then sent in again. This may have to be repeated. Fibrillation is sometimes replaced by standstill. Massage is continued throughout. Epinephrine, one cubic centimeter diluted, and calcium chloride five per cent solution are valuable after fibrillation has stopped. These drugs are given into the right ventricle and massaged around into the coronary arteries. The improvement in tonus is easily felt by the hand. The heart begins to squirm and then starts up with a co-ordinated rhythm. Small doses of epinephrine given in an intravenous drip might be indicated after the rhythm has been restored.

How can defibrillation of the ventricles be made into something more than a physiological demonstration? The methods for success exist. We must apply them and to do so we must bend ourselves to the requirements of the task. In the first place, the surgeon himself turns from the operation to immediate massage of the heart. At the same time oxygen is given intermittently into the lungs. In the second place, someone trained in the use of drugs on the heart must come into the work. Special training is necessary for this. It can be gotten only in the laboratory. It seems to me to be highly desirable to have a resuscitation squad as part of every surgical service. These men would have been taught to defibrillate the ventricles and also the use of drugs on the heart by means of animal experimentation.

COMPRESSION OF THE HEART

A convenient classification for diseases of the heart, especially for the surgeon, consists in classifying them into the group of intrinsic lesions and the group of extrinsic lesions. The extrinsic cardiac lesions are of special interest to the surgeon because they consist of mechanical dislocations, torsions and compressions that are amenable to operative treatment. In my experience

these extrinsic lesions occur as entities, i.e., a compressed heart is not also angulated or rotated and an angulated heart is not also compressed. Traction upon adjacent structures through adhesions to the heart is not included as a component of extrinsic cardiac lesions. In my experience it is doubtful whether traction in the long axis of the heart can disturb cardiac function. If this supposition is correct, and there is good experimental and clinical evidence to support it, the hypothesis of Brauer and the operation of Brauer are no longer tenable. As a rule, an extrinsic lesion does not extend into the heart and become intrinsic. A heart with an extrinsic deformity is to be considered as a good heart that has become crippled by an outside factor. It follows from this that if the extrinsic factor can be removed by operation the heart becomes normal. This result is customarily obtained, although I have seen a few exceptions to it, in conditions in which scar tissue extended into the myocardium from the outside. Likewise it can be stated that intrinsic disease, as a rule, does not become extrinsic. The adhesions that develop in rheumatic heart disease or over a myocardial infarct, both originating from intrinsic lesions, do not disturb cardiac function. These statements, originated by the author, are based largely upon experiences in experimental heart work. They should help to remove the confusion that now exists in nomenclature, diagnosis and operation.

The compression scars are always extrinsic in origin. They never develop as a sequel or complication of an intrinsic lesion. They never originate from rheumatic heart disease. The infection finds entrance into the pericardium from the pharynx, lungs, pleura or mediastinum. In my series of operated cases, seven showed evidence of tuberculosis in the scars and thirty did not show evidence of tuberculosis in the scar removed at operation. Two of this group of thirty patients, however, had tuberculosis elsewhere without showing tubercles in the scar.

The triad of Beck (21) has made the diagnosis simple and infallible. The syndrome has been greatly simplified by placing emphasis upon compression and by eliminating the old fallacy that the heart pulling upon adjacent structures through adhesions

results in dilatation, hypertrophy and failure of the organ. That the compressed heart is entirely free from any of the assumed mal effects of pulling upon adhesions, even though adhesions are everywhere present, has been demonstrated beyond any reasonable doubt. The diagnostic triad consists of (1) a small quiet heart, (2) a high venous pressure in the arm and (3) ascites and a large liver. The diagnosis often can be made by inspection alone. The precordium is quiet. Under the fluoroscope, the pulsation is reduced in amplitude. The sounds are distant. There are no murmurs. One would not expect murmurs in one of the extrinsic forms of heart disease. The venous pressure in the arm may be as high as 42 cms. of physiological solution of sodium chloride. Usually this pressure measures from 20 to 32 cms. It indicates stasis in the superior vena cava. The enlarged liver and ascites indicate stasis in the inferior vena cava. Many manifestations of secondary importance can be mentioned. These are dilatation of the veins, cyanosis, increase in circulating blood volume, depletion of oxygen in the venous blood, reduction in the protein content of the blood, increase in the cerebro-spinal fluid pressure, increase in lymphatic and thoracic duct pressures, subcutaneous edema, hydrothorax, pulmonary edema, a narrow pulse pressure (systolic pressure commonly 100 mm. Hg., diastolic pressure 80 mm. Hg.), reduction in cardiac output, malnutrition and weakness. The muscle fibers in the compressed heart are definitely smaller than normal as shown in recent studies by Dr. Roberts and myself (22). The heart undergoes atrophy of disuse and requires weeks or months to regain its normal strength after resection of a compression scar. The size of the entire heart is smaller than normal. This was demonstrated in cardiac compression produced experimentally (23). That the heart gets larger after resection of the scar was demonstrated repeatedly in patients who were operated upon. The compressed heart is an efficient organ. It does not waste energy. It does not receive a normal quota of blood, but what it receives is propelled by the heart without abnormal resistance or obstruction. The electrocardiogram shows a reduction in voltage. In some cases the heart is fixed to the diaphragm or sternum and in some cases

it is not fixed. Fixation of the compressed heart is of no significance.

As a rule, cardiac compression does not assume any importance to the patient until ascites forms. In our experiments ascites was first noticed when the venous pressure rose to 15 cms. The lowest venous pressure in any of my patients with ascites was 20 cms. The venous pressure can be regarded as an accurate measurement of the pressure upon the heart. Pressures of 8 to 10 cms. on the heart are well tolerated if the pressure is built up slowly. An increase in circulating blood volume takes place in response to the compression and this, in turn, raises venous pressure, which, in turn, injects sufficient blood into the heart to maintain a satisfactory circulation. The venous pressure must always be higher than the compression forces on the heart. The truth of this statement is obvious and it can be considered as a physiological law. If the pressure upon the heart were greater than the pressure in the venae cavae, blood could not enter the heart.

The only treatment for compression scars is operative. If the patient is febrile it is advisable to wait until the infection becomes quiescent. It may not become quiescent and the patient may become so emaciated that operation must be carried out in the presence of active infection. The patient is dehydrated in preparation for operation. When fluid is taken from the abdomen the venous pressure falls and the pressure differential, so essential for filling of the heart, is sometimes reduced to a dangerous level. To elevate the venous pressure and to ensure cardiac filling, an abdominal binder is used as the fluid is removed. Avertin and other basal anesthetic agents should not be used because, with these drugs, respiration might stop. We use a small dose of morphine and nitrous oxide together with a small amount of ether. The anesthetic should be light and must be carefully given. The incision that I use is transverse below the left nipple. The pectoral muscle is exposed and is cut across its fibers about 1 cm. from its origin. The 4th and 5th, and sometimes the 3rd or 6th costal cartilages are completely removed. The left pleural sinus is dissected from the scar. The scar is

incised from apex to base and is separated from the heart as extensively as possible. It should be incised well up over the base of the heart. The separation may be easy or difficult. It may require sharp dissection. As much of the scar is excised as can be safely done. The scar posterior to the heart does not need to be taken away. The things to be avoided are pressure upon a coronary artery, cutting a coronary artery, tearing the ventricle or auricle and dislocations of the heart. If the heart is irritable, rapid or irregular, rest periods are necessary. Procaine applied locally can be useful if the heart is responsive to surgical stimuli from its surface. Anoxemia of the heart is dangerous and should be corrected if possible. The heart dilates after the compression is released. One likes to see this because it indicates release of compression. At the same time, if the dilatation is extreme, the heart might stop. At this point the anesthetist must be careful not to blow up the lungs forcibly because the pulmonary resistance is thereby increased and the right ventricle dilates further. Reduction of venous pressure by venesection might be indicated from this point on. I have not done venesection, but I shall if it is indicated. The left pleural cavity is opened to provide internal drainage. After operation fluid is aspirated from the pleural cavity as necessary. Open drainage to the outside is always contraindicated. The pectoral muscle is sutured in place. Air is sucked from the mediastinum and pleural cavity through a catheter while closure is carried out. Schmieden, Sauerbruch, Winkelbauer, Denk, Westermann, Volhard and Fischer recommend removal of the pectoral muscle and the bony precordium so that when the heart becomes adherent to the chest wall, it will have only skin to pull upon. This is an attempt to combine the Brauer operation with the removal of the compression scar. These authors believe the pull upon adhesions is a factor in this condition. Dilatation and hypertrophy of the heart, which are supposed to result from adhesions, are thus combined in the same organ with the atrophy of compression. The excellent results that can be obtained without removing the pectoral muscle and bony precordium indicate to me that this paradoxical belief must be fallacious. The same

statement can be made concerning the suggestion of Payne, Sauerbruch, Fischer and Schmieden, also other German authors, that the left diaphragm be paralyzed by cutting the phrenic nerve. Complete recovery can be obtained without paralysis of the diaphragm. After operation the patient is placed in semi-Fowler's position in an oxygen tent. Fluid is not given except as requested by the patient. Tachycardia and irregularities in the pulse are treated by digitalis and quinidine.

Improvement is always noted during and after operation. Sometimes the early improvement is lost after several hours because of the dilated, atrophic condition of the heart. Usually the patient feels better as soon as he becomes conscious. He breathes more easily. His hands and feet are warmer than they were before operation. The veins are less distended. Diuresis sometimes begins early; sometimes it is delayed weeks or months after operation, until the heart recovers from its atrophic condition (24). Results: Analysis of literature and private communications shows that 177 patients with compression scars were operated upon by 51 surgeons. Of these Beck had 37 (1939), Schmieden 22 (1937), Blalock 14 (1939), Churchill 12 (1936), Tengwall 7 (1938), Heuer 7 (1939), L. Rehn 4 (1920), de Quervain 4 (1934), Sauerbruch 4 (1925), Borchardt 4 (1938), Läwen 3 (1928), Völker 3 (1933), Whittemore 3 (1935), Budisavljevic 3 (1931). The number of patients listed as cured was 74, or 41.8 per cent; as improved, 41, or 23.2 per cent; as not improved, 1, or 0.5 per cent; as not classified, 4, or 2.3 per cent; and as died, 57, or 32.2 per cent. It should be pointed out that the majority of these patients can be completely cured by operation. Of my series of 37 patients operated upon, 24 are completely free of ascites and edema and can be classified as cured; 3 additional cases have been operated upon recently and probably will be cured; 3 patients were improved and 7 died. Of the 3 patients improved, 1 has invasion of the myocardium by scar, 1 had reformation of calcium deposits around and in the myocardium and 1 had an incomplete operation (a second operation should be done on this patient). Of the 7 deaths, 3 had active tuberculosis in the pleurae and mediastinum, 1 had an

epicardial scar plus bloody fluid and died of infection, 2 died of heart failure from atrophy of the heart, and 1 of ventricular fibrillation during operation. At the present time we are prepared to defibrillate the ventricles at the time of operation.

The dislocations and torsions of the heart constitute a separate subject, which I shall not attempt to discuss.

REFERENCES

(1) Hudson, Charles L., Moritz, Alan R., and Wearn, Joseph T.: The Extracardiac Anastomoses of the Coronary Arteries. J. Exper. Med., **56**: 919, 1932.

(2) Moritz, A. R., Hudson, C. L., and Orgain, E. S.: Augmentation of the Extracardiac Anastomoses of the Coronary Arteries through Pericardial Adhesions. J. Exper. Med., **56**: 927, 1932.

(3) Beck, C. S., and Tichy, V. L.: The Production of a Collateral Circulation to the Heart. I. An Experimental Study. Am. Heart J., **10**: 849, 1935.

(4) Moritz, A. R., and Beck, C. S.: The Production of a Collateral Circulation to the Heart. II. Pathological-Anatomical Study. Am. Heart J., **10**: 874, 1935.

(5) Beck, C. S.: The Development of a New Blood Supply to the Heart by Operation. Ann. Surg., **102**: 801, 1935.

(6) Mautz, F. R., and Thornton, J. J.: Experimental Methods for Producing Chronic Progressive Coronary Arterial Occlusion. To be published.

(7) Phelps, Kenton: A New Method for Producing Gradual Occlusion of an Artery. To be published, Proc. Soc. Exper. Biol. & Med.

(8) Feil, Harold, and Beck, Claude S.: The Treatment of Coronary Sclerosis and Angina Pectoris by Producing a New Blood Supply to the Heart. J. A. M. A., **109**: 1781, 1937.

(9) Brooks, B., Johnson, G. S., and Kirtley, J. A., Jr.: Simultaneous Vein Ligation; Experimental Study of Effect of Ligation of Concomitant Vein on Incidence of Gangrene Following Arterial Obstruction. Surg., Gynec. & Obst., **59**: 496, 1934.

(10) Edwards, M. E., and Holman, E.: New Principle in Surgery of Large Vessels; Ligation of Vein Proximal to Site of Ligation of Artery: Experimental Study. J. A. M. A., **88**: 909, 1927.

(11) Gross, Louis, Blum, Lester, and Silverman, Gertrude: Experimental Attempts to Increase Blood Supply to the Dog's Heart by Means of Coronary Sinus Occlusion. J. Exper. Med., **65**: 91, 1937.

(12) Gregg, D. E., and Dewald, D.: Immediate Effects of the Occlusion of Coronary Sinus Ligation on Dynamics of Coronary Circulation. Proc. Soc. Exper. Biol. & Med., **39**: 202, 1938.

(13) Gregg, D. E., and Dewald, D.: Immediate Effects of the Occlusion of

the Coronary Veins on Collateral Blood Flow in the Coronary Arteries. Am. J. Physiol., **124**: 435, 1938.

(14) Thornton, J. J., and Gregg, D. E.: To be published.

(15) Prevost, J. L., and Battelli, F.: Sur Quelques Effets des Décharges Électriques sur le Coeur des Mammifères. Comptes Rendus des Séances de L'Académie des Sciences, **129**: 1267, 1899.

(16) Hooker, D. R., and Kehar, N. D.: Carbohydrate Metabolism of the Heart during Ventricular Fibrillation. Am. J. Physiol., **105**: 246, 1933.

(17) Kehar, N. D., and Hooker, D. R.: Evidences of an Altered Tissue State in Ventricular Fibrillation. Am. J. Physiol., **112**: 301, 1935.

(18) Wiggers, C. J.: Cardiac Massage Followed by Countershock in Revival of Mammalian Ventricles from Fibrillation Due to Coronary Occlusion. Am. J. Physiol., **116**: 161, 1936.

(19) Wiggers, C. J., and Associates: Studies of Ventricular Fibrillation Caused by Electric Shock: I. The Revival of the Heart from Ventricular Fibrillation by Successive Use of Potassium and Calcium Salts. Am. J. Physiol., **92**: 223, 1930. II. Cinematographic and Electrocardiographic Observations of the Natural Process in the Dog's Heart; Its Inhibition by Potassium and the Revival of Co-ordinated Beats by Calcium. Am. Heart J., **5**: 351, 1930. III. The Action of Antagonistic Salts. Am. J. Physiol., **93**: 197, 1930.

(20) Mautz, F. R.: Reduction of Cardiac Irritability by the Epicardial and Systemic Administration of Drugs as a Protection in Cardiac Surgery. J. Thoracic Surg., **5**: 612, 1936.

(21) Beck, C. S.: Two Cardiac Compression Triads. J. A. M. A., **104**: 714, 1935.

(22) Roberts, Joseph, and Beck, C. S.: Size of Muscle Fibers in Chronic Compression of the Heart. To be published.

(23) Beck, C. S., and Griswold, R. A.: Pericardiectomy in the Treatment of the Pick Syndrome; Experimental and Clinical Observations. Arch. Surg., **21**: 1064, 1930.

(24) Beck, C. S.: The Compressed Heart—Physiology, Clinical Manifestations, and Operative Treatment. The Texas Medical Record and Annals, February, 1939.

The Rickettsioses of North America*

By R. E. Dyer, M.D.

U. S. Public Health Service, National Institute of Health, Washington, D. C.

Certain bacteria-like bodies which are found in arthropods and animals are now generally recognized as living organisms and have been placed in the genus Rickettsia. These rickettsiae may be defined as small gram-negative microörganisms, usually coccoid or bacillary in shape, which stain blue or bluish with Giemsa and are found typically in arthropods. Some of the members of this genus are pathogenic for animals. In both arthropods and animals the pathogenic rickettsiae usually occupy an intracellular position. They have not as yet been cultivated on artificial media free from living cells but multiply readily on various types of tissue cultures such as the chorioallantoic membrane or the yolk sac of the developing chick and some of the basic artificial media to which living tissue has been added. In general, the rickettsiae are not filterable through the common bacterial filters. As far as the relationship of rickettsiae to other disease agents is concerned, it is convenient to think of them as lying midway between the true bacteria and the viruses, being separated from the one by their non-cultivability on ordinary media and from the other by their visibility.

The type rickettsiae pathogenic for man are: *R. prowazeki* of typhus fever, *R. rickettsii* of Rocky Mountain spotted fever, *R. nipponica* of tsutsugamushi, and *R. quintana* of trench fever. Two recently described rickettsiae, *R. burneti* of "Q" fever, described by Derrick and Burnet, of Australia, and *R. diaporica*, recently described in Montana, may be tentatively accepted since they are within the definition of rickettsiae, although they lack one characteristic of the other rickettsiae in that they are

* James M. Anders Lecture XIV, The College of Physicians of Philadelphia, November 1, 1939.

readily filterable, while the diseases with which they are associated show some clinical and serological differences which may challenge their admission to the group. The relationship of trench fever to the other rickettsioses is not well understood, as this disease has apparently disappeared since the last World War and no thorough comparison has been made between it and the other members of the group.

Based on morphology and staining, rickettsiae or rickettsia-like bodies have been described in psittacosis and trachoma, but there is no satisfactory evidence that these rickettsia-like bodies have been found in or can be transmitted by arthropods, although some workers have reported results which would indicate the possibility of growth of the trachoma virus in lice. For the purpose of this discussion, at least, we can eliminate both psittacosis and trachoma from further consideration.

In addition to the rickettsioses already named, human diseases which belong to this same group have been described in many sections of the world. These diseases have often been given local names or names suggestive of some outstanding characteristic. A few of them have already been identified with, or had a close relationship shown to, one of the three well-defined members of the group. Thus we have Sao Paulo exanthematic typhus of Brazil, which has been identified with Rocky Mountain spotted fever; boutonneuse fever of the Mediterranean littoral, which, immunologically, is closely related to spotted fever; Kenya typhus of East Africa and its suggested relationship to boutonneuse fever. The tick typhus of India, the disease in South Africa called tick fever, and the so-called typhus of Minas Geraes in Brazil may all ultimately be shown to belong to the spotted fever sub-group since the evidence at present indicates that each is transmitted by ticks.

The mite-borne group is, so far, limited to tsutsugamushi, with which the scrub typhus of the Federated Malay States has been identified, and there is the further probability that the pseudo typhus of Sumatra belongs in the same category.

There are two recognized forms of typhus, each of which has borne many names. The louse-borne disease may be referred to

as classical, exanthematic, and epidemic typhus, while the flea-borne form is variously referred to as American, rat, shop or urban, murine, and endemic typhus. In this paper the names epidemic typhus and endemic typhus will be used to refer to the louse-borne and flea-borne type, respectively.

The two already-mentioned diseases caused by *R. burneti* and *R. diaporica*, although probably correctly assigned to the rickettsioses, may constitute a fourth sub-group. Apparently both are tick-borne and, although described from widely separated parts of the world at about the same time, have already been shown to be immunologically closely related to each other and distinct from the other rickettsioses.

If we take as one of the criteria for the classification of rickettsiae their presence in and transmission by arthropods, we find that the diseases caused by them have certain definite similarities. First, the epidemiology of these diseases or rickettsioses is determined by the life history and feeding habits of its particular arthropod vector. Second, the rickettsioses are clinically similar, being characterized by fever and exanthem. Third, in human beings and some animals these diseases produce agglutinins for the OX proteus strains first described by Weil and Felix.

The explanation of the agglutination of Proteus X strains by the sera from these diseases is not well understood. It has been fully shown that these Proteus strains are not the causative agents in these diseases, although some authors consider them variants of rickettsiae and explain the Weil-Felix reaction on that ground. Another view is that the Weil-Felix reaction is an example of paraagglutination. Recent work by Castaneda showing that Proteus X and *R. prowazeki* have an alkali stable polysaccharide in common may ultimately lead to an acceptable explanation of this reaction. For the moment we can only accept the fact of the agglutination and its value as a diagnostic test. There are two antigenic types of Proteus X—OX-19 and OX-K—which agglutinate with the sera of different groups of the rickettsioses. Thus, OX-19 and its companion strain OX-2 agglutinate with the sera of typhus and Rocky Mountain spotted fever patients, while OX-K agglutinates with tsutsugamushi sera. Occasionally

spotted fever sera show some agglutinins for OX-K. Immunologically, typhus, spotted fever, and tsutsugamushi may be distinguished, since cross immunity and cross protection is lacking among them.

Efforts have been made to classify the rickettsioses on the basis of the agglutination of different strains of proteus, but this is not altogether satisfactory, since two of these diseases, typhus and spotted fever, although distinct epidemiologically and immunologically, do not produce clearly-differentiated agglutinins and it is reported that "Q" fever does not agglutinate any of the known strains of Proteus. Another suggested method of classification is based on the genus of the arthropod vector. This may not prove satisfactory, since there is an immunological difference between the "Q" sub-group and spotted fever, while each is tick-borne. It seems probable that for the present, at least, we should reserve decision on any classification for the various rickettsioses until future investigations develop a sound basis for such classification.

Of the rickettsioses mentioned above two are endemic in North America, typhus and Rocky Mountain spotted fever.

TYPHUS FEVER

There are two varieties or types of typhus fever. These two types are clinically similar, give complete cross immunity with each other, and are serologically identical as far as can be determined by the Weil-Felix reaction, but show a distinct epidemiological difference due to transmission by different arthropods whose life histories are dissimilar. The louse-borne type is epidemic in character, while the flea-borne type is sporadic or endemic. Lice are more prevalent in winter and spring and fleas more common in summer and fall, hence, epidemics of typhus are more apt to occur in the colder months and the endemic flea-borne cases in the warmer months. The common rat is a reservoir for the endemic form of typhus, the disease being transmitted from rat to rat and to man by the common rat fleas, the rat louse also assisting in rat to rat transfer. There are two general views of the relationship of these two forms of typhus. One view

is that the causative rickettsiae originally developed from a common stem and have since been perpetuated as distinct types. The other view is that rat typhus is the parent type and that the epidemic type develops from that under favorable conditions. One theory would explain the perpetuation of epidemic typhus by the occurrence of mild unrecognized cases during interepidemic periods, while the second theory presents the rat as a constant reservoir from which the disease may be passed to man by the rat flea and then from man to man by the human louse. It is conceivable that both factors may play a part in the perpetuation of the disease and the formation of epidemics.

Strains of virus isolated in animals from the two types of typhus show some differences which have not been explained. The endemic strains, whether isolated from epidemiologically typical human cases, from rats or from fleas, produce in guinea pigs a shorter, more irregular febrile reaction than do the classical epidemic strains. In addition, the endemic strains characteristically produce a swelling of the testicles of male guinea pigs, an edema of the subcutaneous tissues of the scrotum and a marked erythema of the overlying skin. This reaction is quite definite and usually appears with the fever and disappears in four or five days when defervescence occurs. A mild reaction of this type occurs in occasional guinea pigs infected with epidemic strains, but does not reach the same intensity and is seldom in evidence more than 24 to 36 hours. Further differences in other species of animals have been noted by various workers. The epidemic virus produces an inapparent infection in rats and cannot be maintained in mouse passages while the endemic virus produces a fever in rats and can be maintained indefinitely through passage from mouse to mouse.

Epidemic typhus

For the purposes of this discussion we can dismiss epidemic typhus with the statement that this form of the disease has been introduced into various Atlantic and Gulf seaports from time to time in connection with immigration and at times has caused small, self-limited epidemics but has never established itself here as a louse-borne disease.

Brill's disease

Approximately forty years ago Brill first brought to light cases of the disease which still bears his name and which was identified as being immunologically identical with classical epidemic typhus by Anderson and Goldberger in 1912. Brill's studies were limited to cases occurring in New York, but similar cases occur each year in Boston and other northern seaports in addition to New York. There is no evidence that these cases are louse-borne. Zinsser has pointed out that these cases of Brill's disease occur predominantly among immigrants, particularly Jewish immigrants, and of these, those from Russia furnish the larger share of cases. Zinsser further studied strains of typhus isolated in Boston and New York and found that in laboratory animals these strains produce the picture characteristic of epidemic typhus. Efforts have been made to isolate typhus virus from rats in New York City with no successful results, although Nigg reported finding weakly positive Weil-Felix reactions in 16 of 51 wild rats trapped in New York City and some evidence that injection of brain from some of these rats into guinea pigs had some immunizing effect.

Zinsser has advanced the theory that Brill's disease is an imported classical typhus which has become endemic in immigrant populations and that cases of this disease are recrudescences of attacks suffered prior to immigration. Similar cases occur in small numbers each year in the other large seaports as far south as Baltimore and their exact relationship to the typhus of the southern states is not as yet definite. However, it should be noted that strains showing the characteristics of endemic typhus strains have been repeatedly isolated from rats and fleas trapped in areas in Baltimore, which, from epidemiological observations, have been the source of human cases.

Endemic typhus, history and distribution

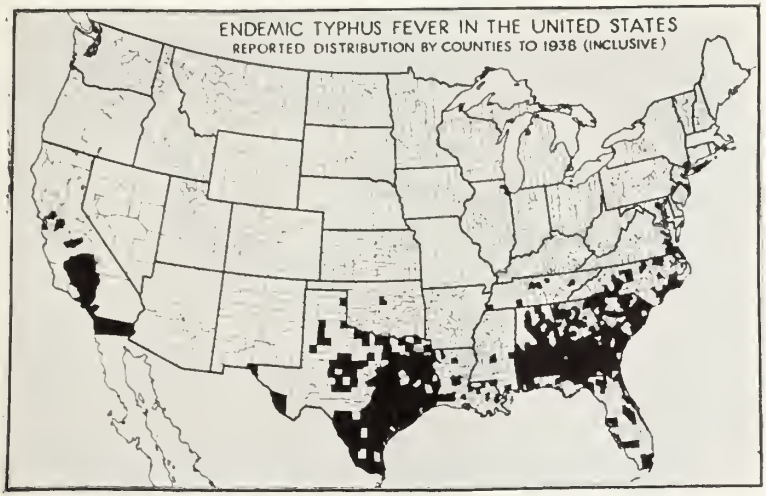
Endemic typhus was first reported in the south at Atlanta, Georgia, in 1913 by Paullin. Other reports followed in the next few years—Charlotte, North Carolina, 1914; Galveston, Texas, 1916; and others. In 1923 Maxcy and Havens reported a number of cases in Alabama. These cases were identified as being

immunologically and serologically identical with classical typhus. The epidemiological features brought out by Maxcy and indicating the rat as a reservoir are too well known to need any discussion here. It may be said that since Maxcy's first epidemiological study in 1926 no facts have been brought to light in subsequent studies in our southern states which question the transfer of typhus from a rodent reservoir to man by the rat flea, more probably through the medium of the flea feces than through the bite of this arthropod.

In 1929 the human cases of endemic or murine typhus were practically limited to the towns, particularly those along the southern Atlantic coast from Baltimore south and continuing along the Gulf coast and up the Rio Grande as far as El Paso, with a few cases in Southern California. Towns in the interior of the southern states were likewise affected but to a lesser extent as the distance from the seaboards increased. As late as 1932 the northern limit of the disease in Alabama was about in a line with Montgomery. Since 1932 cases have appeared further north until at present the known northern limit of the disease has reached central Tennessee. The accompanying map (Map I) gives the present known distribution. Coincident with this geographical extension of typhus there has been an extension to the rural districts. This was first noted in Alabama and Georgia in the so-called peanut belt and has more recently been noted in Texas. In Alabama it is estimated that 30 per cent of the typhus cases occur in strictly rural areas. Hendrick makes the statement that 84 per cent of the cases in Worth County, Georgia, are rural. Texas also shows a spread of the disease from the towns to the country in certain sections. Various suggestions have been advanced to account for the loss of the strictly urban character of our endemic typhus. Foremost among these is the part played by the increasing acreage planted in food crops in the southern states in recent years. This has resulted in the storage of food stuffs on the farms, which was practiced in relatively small degrees prior to 1929. This storage of food on farms, earlier given over to the cultivation of cotton, presumably has tempted the rats from the towns and cities. However, it is very difficult to get

any reliable data on such migrations. Oldsters among the farmers of the affected sections, although claiming a long acquaintance with native wood rats, state that the wharf rat is a recent arrival on their farms. Newspaper items such as that quoted below have appeared from time to time. This extract from the *Atlanta Journal* of June 12, 1939, is as follows:

"The farming community of Lundberg, Wilkes County, was victim recently of an unwelcome invasion. A legion of wharf rats appeared, destroying hundreds of chickens and causing other damage."



Map I

Just how much weight can be given to such evidence it is hard to say. However, an infiltration of the rural areas by rats from typhus foci in towns would amply explain the spread of typhus to the country. One other factor probably explains some of the rural cases and surely plays a part in keeping the disease alive in nature, namely, the proven presence of the infection in a species of native field mouse which is rather widely distributed along the Gulf coast. The most important rodent reservoir and surely the first observed is the gray rat. Apparently the infection has spread to one species of field mouse and other species of rodents

may already be infected, since Brigham has shown that several native species are experimentally infectible.

How long this disease has been present in this country it is impossible to say. It surely was present many years before it was recognized. It is also true that, beginning with 1923, the physicians have become more and more conscious of typhus, which has naturally resulted in a wider recognition of cases and which must be taken into account in following the prevalence of the disease during the years. In 1925 about 150 cases were recog-

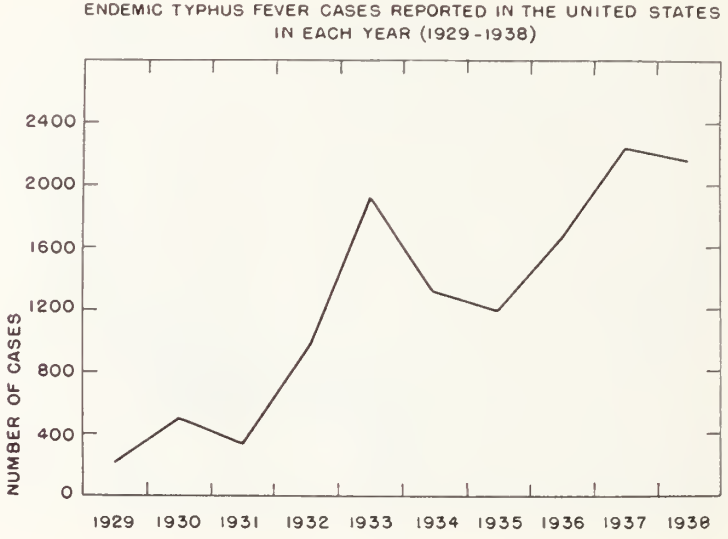


Chart I

nized and reported for the United States. This number was increased slowly each year until 1929 when 250 cases were reported. The number doubled the next year but receded to 350 in 1931. Two years later the reported cases numbered 1922. This was followed by a two-years decrease, the number in 1935 being 1195. This decrease in cases followed extensive rat-poisoning campaigns in Georgia, Alabama, and Texas, the three states reporting the greatest incidence of typhus. Since this poisoning of rats was carried out over wide areas and no control areas were set up, it was not clear that the decrease in the number of reported cases

during 1934 and 1935 was the direct result of the destruction of rats. However that may be, it does give an indication that the rapid increase in reported cases during the two preceding years could not be entirely explained on the basis of increased recognition.

Chart I shows the reported incidence of typhus each year for the last ten years.

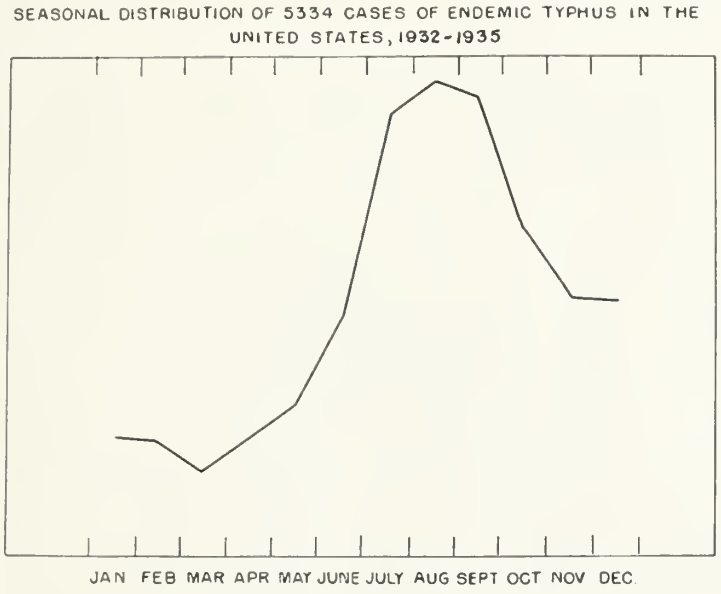

SEASONAL DISTRIBUTION OF 5334 CASES OF ENDEMIC TYPHUS IN THE UNITED STATES, 1932-1935
JAN FEB MAR APR MAY JUNE JULY AUG SEPT OCT NOV DEC

Chart II

Typhus remains a disease particularly of the late summer and fall, although no month is free. Chart II shows the seasonal distribution based on 5334 cases during the years 1932–1935, inclusive.

Chart III gives the seasonal incidence of cases during each of the last five years shown in the following chart.

It may be noted that there is a tendency for the peak season to fall somewhat later in the latter part of the five year period. This is at least partially explained by a point recently brought out by Kemp in a discussion of typhus in Texas. This state

shows a peak for the cases in the northern section of the state approximately two months later than the peak in the southern part of the state. If this proves true for other sections, we can expect a broadening of the peak as the disease spreads northward. Such a finding appears in the last two years shown in Chart III.

From the available figures there is little noteworthy change in the age and sex incidence. All ages are affected with the greatest incidence in the years 11 to 39, this period accounting for over half the cases.

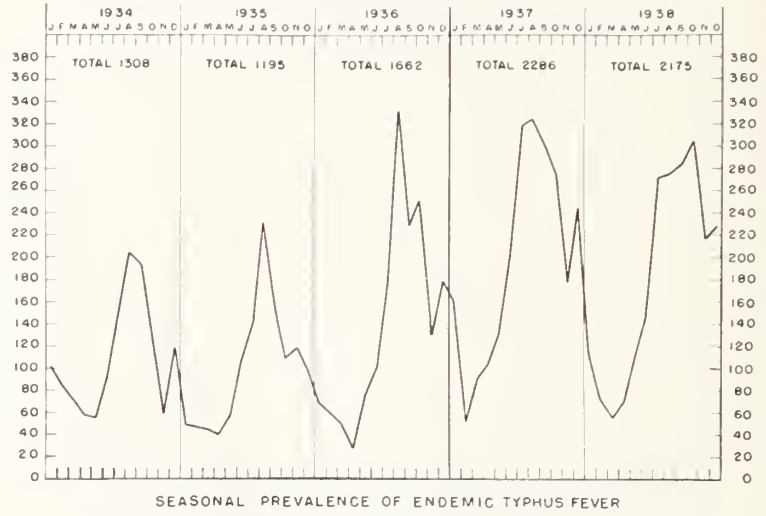


Chart III

Males are more often attacked than females. Kemp gives the figures in Texas as approximately four males to one female. Further east the ratio is about two to one. This, as well as the age distribution, is to be expected, as male workers in the store and on the farm are more exposed to contact with rats than housewives and children. In general, these features of typhus are the same as those described by Maxcy in 1926. Only in one particular is there noteworthy variation from his reports. He failed to find cases in negroes. This may have been due to the comparatively small number of cases reported in the years of

his study, or cases among negroes may be, in fact, an extension of the past few years. Beginning with 1932 the colored race has furnished a little under 10 per cent of the reported cases. The rate of increase in this race has been somewhat more rapid than in the white race, but the discrepancy is not wide enough to warrant comment.

Clinical picture

In a few cases in which the incubation period in endemic typhus could be determined with some degree of accuracy it varied from 6 to 14 days. The onset may be preceded by poorly defined prodromata for a few days, but in the majority of cases the disease begins suddenly with a chill, or repeated chills or chilliness, fever, headache and prostration. The appetite is lost and constipation is the rule.

The fever rises steadily, each day's maximum exceeding that of the previous day, the highest point being reached in from 3 to 6 days. Morning remissions of from 1° to 3° F. occur. The fever terminates usually by rapid lysis about the end of the second week, most often on the fourteenth day, the great majority being afebrile by the sixteenth day.

The eruption most often appears on the fifth day, occasionally being noted as late as the seventh. It appears first on the inside of the upper arms, or sides of the chest and on the upper abdomen. No extension of the rash from this location may be noted in some of the cases. In one case a total of seven macules was noted, while a second at no time presented more than a dozen and a half lesions. In more pronounced cases the development of the rash is rapid during the first 24 hours after its appearance. In cases showing a well-marked rash the eruption is also present on the shoulders, over the back, and may extend down the forearm, usually leaving the wrists and hands free. Occasionally in severe cases the rash may involve the thighs and the palms. The rash usually stops at the knees, although occasionally the lower legs, feet and soles may be affected. The face and neck are seldom involved. The rash in the mild cases may persist only two or three days and in the majority of cases disappears by the time the

temperature reaches normal. In rare cases the rash may persist as discolorations for a week or ten days after defervescence. These discolorations may be especially noticeable after taking a warm bath.

The eruption consists of macules rose-red in color and 2 to 3 mm. in diameter with rather poorly defined margins. The lesions fade on pressure but may not completely disappear. In the severe cases the individual macules become petechial fairly early. Occasionally some of the lesions may be maculo-papular and occasional cases have been described in which no rash was observed during illness.

The pulse is apt to be slow, seldom exceeding 100, even with a high temperature. During early convalescence the pulse may remain for several days below sixty. This slow pulse may be supplanted by a rate higher than normal for a few weeks after moderate activity is resumed. After severe attacks shortness of breath on moderate exertion may be present for a few weeks, suggesting a myocardium weakened by toxaemia.

Headache is almost always present from the beginning. It may involve the whole head but is more commonly frontal and is quite often intense, lasting throughout the illness. In other cases headache may never be distressing, being present only a few days. It is occasionally absent throughout the disease.

Some degree of mental disturbance is common. This may vary from vivid and not easily forgotten dreams to mild delirium in rare instances. Confusion and disorientation are more apt to be present at night. Lethargy, restlessness, insomnia, irritability may be noted. Tremors and, in severe cases, subsultus may occur.

Generalized aching is often present. Some evidence of respiratory inflammation is common, often showing as a mild unproductive cough. Prostration may be present from the onset and in severe cases becomes quite marked during the second week. Constipation is usually present throughout the course of the disease. Photophobia and soreness of the eye-muscles may occur. Slight chills followed by sweats are not uncommon at night. Complications are rare and convalescence in mild cases

is speedy. Following the more severe cases normal strength may be regained slowly. In any event, recovery is complete.

The case fatality is estimated at less than two or three per cent, practically all the deaths occurring in patients over 50 years of age.

Laboratory findings

Little of significance is shown by examination of the blood. Usually the white count is normal or little reduced. However, occasional cases are encountered with a slightly increased number of white cells. The urine, at the height of fever, may show albumin and occasionally casts.

In practically all cases of endemic typhus agglutinins are developed for Proteus OX-19 and, to a lesser extent, for OX-2. When agglutinins for both these strains are present the titer for X-19 is usually the higher. Agglutinins for OX-K have not been reported in endemic typhus.

Agglutinins usually appear sometime during the second week, rise rapidly in titer, reach their height about the time of defervescence and diminish rapidly during convalescence. Sera from febrile patients not suffering with a rickettsial disease occasionally produce a Weil-Felix which is positive in low titer. While some cases of endemic typhus do not show exceptionally high titers, the usual typhus serum will, at some time during the febrile period, show a titer with OX-19 of over 1:640, while titers of 1:5000 and over are not uncommon. Occasionally sera may titer as high as 1:40,000 or possibly higher. In the sera of patients who do not produce agglutinins in high titer it is important to watch the course of the reaction during the disease and in convalescence, since a waxing and waning titer is characteristic. We have seen sera showing complete agglutination at 1:320 from patients whose clinical symptoms were not suggestive of one of the rickettsioses. One puzzling case may be cited in which complete agglutination of OX-19 occurred at the dilution 1:10240. This patient showed no rash at any time and was otherwise not suggestive of typhus nor of spotted fever. Attempts to recover one of the rickettsia from this patient were not successful. The

above is cited to stress the fact that, after all, the Weil-Felix is a laboratory confirmation of the clinical picture shown by the patient and should not be relied upon alone for diagnosing one of the rickettsioses. From our present knowledge, titers of 1:640 and less on single specimens should not be regarded as diagnostic of a rickettsial infection unless supported by clinical evidence. With the exception of the one puzzling case cited above, we have not observed titers of 1:1280 and over in sera other than from one of the rickettsioses.

Treatment

There is no specific treatment of proven value for endemic typhus and in the great majority of cases none is needed. Rest, quiet, good nursing, with care of particular symptoms such as headache, constipation, and mental disturbances when needed are sufficient. Elderly patients with preexisting heart or kidney conditions should occasion a guarded prognosis.

Identification by animal inoculation

For positive laboratory identification of one of the rickettsial diseases the isolation of the strain from the blood of the patient is essential. In attempting such isolation in suspected cases blood should be drawn from the patient early in the disease. This blood in 4 to 5 cc. amounts may be injected intraperitoneally into guinea pigs and in smaller amounts into rats. Better results may be obtained by allowing the blood to clot and then injecting the clot after macerating it in salt solution. The clinical reactions produced by endemic typhus in guinea pigs have been often described and need not be repeated in more detail than that appearing earlier in this paper. Since guinea pigs do not produce agglutinins for the Proteus OX group, rabbits or monkeys may be subinoculated from passage guinea pigs. Agglutinins in these latter animals seldom exceed 1:320 or 1:640 in titer, but show the same phenomenon of waxing and waning titer that is shown by human cases. Final identification of the virus should be based on crossed immunity tests with known strains of the rickettsial diseases and the histological examination of the brains of animals for the typical pathological changes.

Protection tests carried out on the sera of convalescent cases of endemic typhus are of value if definite results are secured. Since neither the epidemic nor the endemic strains of typhus will kill guinea pigs, it is not often possible to get readable results from protection tests. Other laboratory animals are even less satisfactory for this purpose.

The histological changes in the brains of guinea pigs have been often described. Lillie has pointed out that the number of lesions in infected guinea pigs reaches its peak from 8 to 11 days after inception of fever. As reported by the same author, the brain lesions in guinea pigs infected with endemic typhus consist of more or less compact nodes of glia cells, often situated adjacent to small vessels, and of various vascular lesions. The glia cell nodes are usually composed of small cells with rounded or elongate (rod) nuclei and little evident cytoplasm, sometimes of large round cells of amoeboid glia or monocyte type compactly grouped. They lie in the brain substance, either gray or white, possibly more often in the gray. Not infrequently they occur in the molecular layer of the cerebral or cerebellar cortex. The vascular lesions consist of infiltration of the vessel sheaths, usually by lymphocytes, of swelling and proliferation of adventitial fibroblasts, and of swelling and concentric proliferation of vascular endothelial cells. Thrombosis and endothelial necrosis are rarely seen.

Prevention of endemic typhus

The control of endemic typhus, from our present knowledge, should be based on the control of the rat population—by trapping, poisoning and rat proofing. Of these measures the last is the only one that may be considered as of some permanent value. Trapping and poisoning must be continuous to be of any practical value and are of little temporary value unless backed by an attack on the rat's home and his feeding places by rat proofing.

Vaccines

Various types of vaccines have been prepared for immunization against typhus. Attenuation of the living virus by heat and by

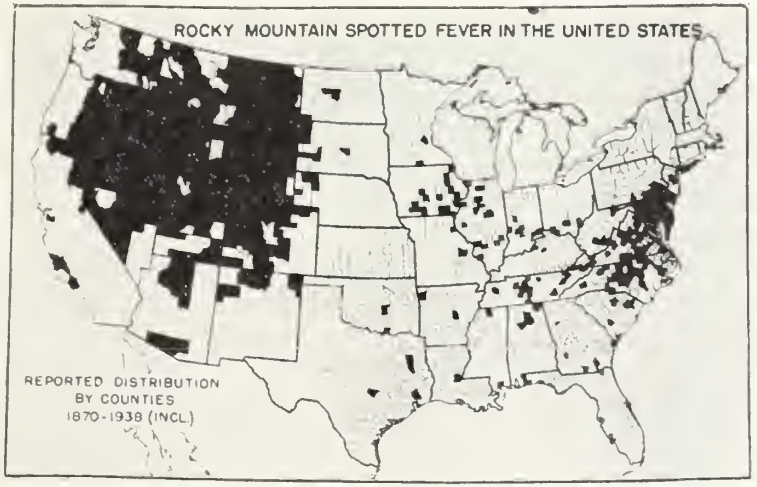
the addition of such substances as bile, as well as partial neutralization of the virus by convalescent serum has been used. However, the dangers inherent in the use of a living virus for immunization should prohibit its use as long as there is hope of securing the same results with a dead product. Several preparations have been made which utilize rickettsiae killed usually by formalin or phenol. One of these methods, that of Weigl, apparently gives good immunity, but unfortunately this vaccine cannot be produced on any very large scale, requiring as it does the rectal injection of lice with suspensions of rickettsiae, the subsequent feeding of the lice on typhus-immunes and the later removal of the louse intestines, a treated suspension of which is used as the vaccine. Approximately one to two hundred lice are needed for the vaccination of one person. Methods advocated by Zinsser and his collaborators and by Kligler and others, in which various methods of tissue culture are employed for the production of rickettsiae, give promise of efficacy and of quantity production. None of these vaccines is available on the market in this country at the present time.

ROCKY MOUNTAIN SPOTTED FEVER

Distribution

The second of the human rickettsioses known to be endemic in North America is Rocky Mountain spotted fever. As the name implies, this disease was first recognized in the Rocky Mountain section, where it has been extensively studied by Wilson, Chowning, Ricketts, Spencer and Parker. Until 1930 the disease was thought to be confined to 11 states of the Northwest although one case in Indiana had been reported in the literature and the diagnosis of spotted fever had been considered in others prior to 1930. During the spring and early summer of 1930 Rumreich and Badger clinically identified the disease and isolated the virus from suspected cases occurring in the eastern states. Since the time of definite identification of the disease in states outside the originally known area, new states or sections of states have been added to the known distribution of the disease each year. At present, study of suspected cases has shown that the area of dis-

tribution includes 41 states, to which may be added at least two of the provinces in Western Canada—British Columbia and Alberta. Five of the New England states—Maine, New Hampshire, Vermont, Connecticut and Rhode Island—have not as yet reported confirmed cases known to have originated in the states. In the Middle West, Wisconsin and Michigan are not known to be infected. The infection has not been definitely recognized in Kansas. The accompanying map (Map II) gives the known distribution of spotted fever in the United States up to and including the 1938 season.



Map II

The number of cases reported each year since the recognition of the fact that the disease is widely distributed over the United States has remained at a figure a little short of 1,000. There is a wide variation in the virulence of the strains of spotted fever as shown by the case fatality rates in human beings. Cases occurring in certain districts—as Southern Idaho—give a case fatality rate of less than five per cent, while in certain sections in Montana the rate sometimes reaches 75 per cent. In the infected areas in the east and in the United States as a whole, the rate is 20 to 25 per cent.

Transmission

Several species of ticks are known to be capable of transmitting Rocky Mountain spotted fever. *Amblyomma americanum*, *Amblyomma cajennense*, *Dermacentor parumapertus marginatus*, *Dermacentor occidentalis*, *Rhipicephalus sanguineus*, and *Dermacentor albipictus*, have been shown to be efficient transmitting agents under experimental conditions. However, the dog tick (*D. variabilis*) together with its near relative the wood tick of the Northwest (*D. andersoni*) are the only two species biting man in which the virus of the disease has been found naturally present. In addition, the distribution and seasonal incidence of these two species adequately explain the epidemiology of the disease. A third tick, the rabbit tick (*Haemaphysalis leporis palustris*), has been found naturally infected, but this species does not bite man; however, it probably plays an important part in preserving and spreading the virus in nature. There is no evidence at present that indicates that any arthropod other than ticks transmits the disease.

The life history and feeding habits of these two Dermacentors (andersoni and variabilis) are similar and a knowledge of them is necessary to explain the epidemiology of the disease.

The life cycle of the Dermacentors comprises four stages, adult, egg, larva and nymph. Unlike some of the other arthropods and indeed some other genera of ticks, the spotted fever ticks normally feed only once in each feeding stage. An occasional adult may become dislodged from its animal host before engorgement is completed and may reattach to another host, but such an occurrence probably does not often happen. From this peculiarity of feeding it will be evident that a disease to be perpetuated by this tick must be passed on from one stage to the next and laboratory experiments show that this is what happens with this tick and Rocky Mountain spotted fever. In other words, this tick may become infected by feeding on an infected host in any one of its feeding stages. The virus is then in many instances passed on through succeeding moults and through the egg to succeeding generations.

The adult ticks feed readily on a large variety of animals rang-

ing in size and species from rodents to man, horses and cattle, most of which have been shown to be susceptible to the disease.

The list of animals that are known to be susceptible to spotted fever embraces several species of squirrels, rats, mice and rabbits, wood chucks and large animals as the dog and sheep. The larvae and nymphs, particularly the larvae, have been found more often on the smaller rodents, especially the various species of wild mice, while the nymphs have also been found on some of the larger animals. Statements from some sections of the country indicate that the nymphs will occasionally feed on man. We know of no records of larvae engorging on man.

The adult ticks emerge from hibernation early in the spring, the exact time of appearance being apparently dependent on the advent of warm days. In the middle Atlantic states the adults usually appear some time in March, reach their peak of prevalence in May, June and early July, declining in numbers rapidly after the middle of July and practically disappearing before the middle of August. Further south the seasonal prevalence is more extended and they may be found in mid-winter.

In the Northwest andersoni usually appears a little earlier than does variabilis in the rest of the country and also disappears a month or so earlier in the summer. The number of ticks apparently varies from year to year. The factors governing this yearly variation are not well understood but heat and drought probably play an important part in reducing their numbers.

The technic of finding a host and attaching is essentially the same for the three feeding stages. The unfed ticks after passing a period of quiescence in the winter under leaves, in tufts of grass and in other protected places, emerge and crawl up on vegetation to await a host. The larvae and nymphs are more often found on low vegetation, while the adults may also be found in bushes and occasionally even in trees. From their waiting places the ticks transfer to animals that brush by. Unlike such insects as the mosquito and the flea, the tick does not immediately start feeding but wanders around on the host, possibly in search of a place where it is not apt to be disturbed during feeding. Preferential feeding sites on man are the hairy portions of the body

and head, although they often attach elsewhere. After the site is chosen the tick attaches and feeds until entirely engorged unless forcibly removed. This is true of all feeding stages save the adult male, which after feeding detaches and searches for a female, copulation taking place during the engorgement of the female. The adult female requires about 8 or 10 days for engorgement, the rate of feeding being somewhat faster in the spring and slower in the summer and fall. In the late fall and winter it is often difficult to get ticks to attach. In the process of engorgement the females increase in size from a length of about $\frac{3}{16}$ of an inch and a breadth of a little less, to a length of about one-half inch with a proportionative increase in width. They also increase in thickness from about $\frac{1}{32}$ inch to approximately $\frac{1}{4}$ inch. The males increase a little in thickness but practically not at all in length or breadth during feeding.

After engorgement and fertilization is complete the ticks drop to the ground, hunt places of concealment similar to their places of hibernation. The female then lays her eggs after a period of quiet of a few days to three weeks. The eggs are produced over a period of about two weeks or a little less, the number of eggs deposited by one female being in the neighborhood of 5000. During oviposition the female shrinks in her antero-posterior diameter until the process is completed, when she crawls away to die within a few days to a month. The larvae begin to hatch about one month after the time the first eggs appear. If suitable hosts are reached the larvae attach and feed within a few days after hatching. Like the adults and nymphs, once attached, the larvae feed until dislodged or completely engorged, this latter process taking about one week. After engorging and dropping from the host the larvae seek a protected spot on the ground and after a somewhat variable period of time moult to the nymphal stage. In general, the time from engorgement of the larvae to moulting varies from two to six weeks, although under optimum conditions of temperature (about 80° F.) the time may be reduced to one week, while under less favorable conditions (temperature about 50° F.) the moulting may be delayed two or thee weeks.

The nymphs, like the larvae and adults, await their host, attach and engorge, usually taking about a week for engorgement. The nymphs moult to adults after a variable period of time depending largely on the temperature. In general, this period varies from about one month in summer to two months or more in winter under laboratory conditions. Sexual differentiation is present only in the adults.

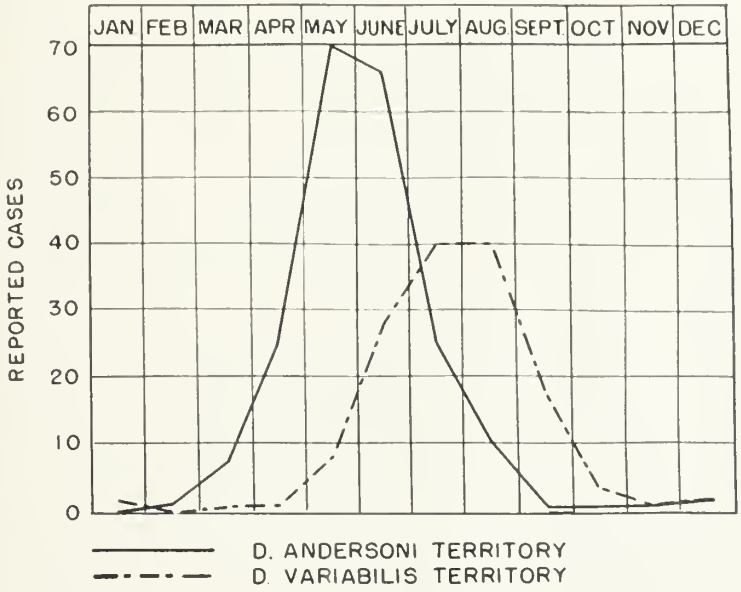


Chart IV

The incidence of human cases of the disease closely follows the prevalence curve of the tick. Consequently, the disease is chiefly a disease of spring and early summer, being somewhat earlier in the Northwest than it is in the East, as may be seen in Chart IV.

Clinical picture

The diagnosis of spotted fever in the human being is usually made on clinical grounds, as definite laboratory proof of infection is a tedious procedure not to be undertaken by the usual clinical

laboratory. In many of the general features, this disease resembles typhus, the chief differential points being the severity of the illness, duration of fever, and time of appearance and location of the rash.

In man the disease has an incubation period of two to twelve days, most often being a week or a little less. As in endemic typhus the actual onset may be preceded by a few days of ill defined prodromata—lost of appetite, listlessness or headache. The onset is usually sudden, with a chill or chilly sensations, and rapidly rising fever. Prostration is usually marked. In the more severe cases, nosebleed may occur early. Soreness of the muscles and joints is commonly present. The temperature rises rapidly and shows morning remissions of 1° to 3° F. The temperature reaches its highest point usually in the second week. The termination is by rapid lysis, usually about the twenty-first day, although mild cases may be afebrile before the end of the second week.

The most distinguishing characteristic of the disease is the rash. This appears between the second and fifth days, usually on the third or fourth. The eruption is macular, rose-red in color at first, and becomes fainter, almost disappearing during the morning remissions of fever early in the disease. The macules become more distinct each day, becoming definitely petechial early in the second week in all but the mildest cases. In the severe cases the spots become deep red or purplish and confluent. Necroses may develop. The rash usually persists throughout the febrile period and into convalescence, becoming brownish in color. A branny desquamation often occurs over the areas where the rash was thickest. The site of the first location of the rash and its spread and final distribution are important in the diagnosis of the disease. The rash first appears usually on the wrists and ankles. It spreads rapidly in the first 24 to 48 hours to the back, then arms, legs, chest, and last to the abdomen, where it is least marked. The palms and soles are frequently involved and occasionally the face and even the scalp is included.

Nervous and mental symptoms are common: restlessness, insomnia, disorientation and, in severe cases, delirium. Coma

usually precedes death, which often occurs about the end of the second week.

Convalescence in severe cases is apt to be slow and may be complicated by visual disturbances, deafness or mental confusion. Although recovery may be delayed, it is usually complete in the end.

Treatment

As in the other rickettsioses there is no specific treatment of proven value. Injections of serum from convalescent cases have been tried repeatedly, as have transfusions from immune donors, without definite benefit. Indeed, it is the opinion of many of those who have had the most extensive experience in the treatment of these cases that intravenous therapy of any kind lessens the chances of recovery. The newer chemicals metaphen, sulphanilamide and sulphapyridine have been tried, without definite evidence of benefit to the patient. Topping has recently reported that the experimental use of sulphanilamide and sulphapyridine in the treatment of spotted fever in guinea pigs increases both the severity of the infection and the death rate.

Good nursing care, avoidance of exertion mental or physical, maintenance of the fluid intake, by mouth preferably, by Murphy drip or hypodermoclysis if necessary, relief of the headache by aspirin, codeine, or morphine give the best results. The mind of the physician may be relieved by the knowledge that there is more danger from overtreatment of these patients than from undertreatment.

The deaths usually occur before the 15th day, commonly from the 8th to the 12th days. If the patient is going to recover, some indication of this may often be found in a slight decrease of the temperature about the 14th or 15th day which becomes more definite with each succeeding day. Final defervescence occurs by rapid lysis which often brings the temperature to normal about the end of the third week. The temperature may rise above normal in the afternoons for a few days longer. If no complications are present, a slow but steady recovery may be expected. After severe infections strength may not be completely regained for

many months. Remnants of the rash may be present for several months. In one case at present under observation the rash is still in evidence ten months after the termination of illness.

Laboratory findings

The clinical laboratory has little to offer in the way of differential diagnosis between spotted fever and endemic typhus. The white cell count is increased in the former disease, usually being about 12,000, although it may be as high as 30,000, which is in contrast to the moderate leucopenia usually seen in endemic typhus.

The Weil-Felix reaction gives no aid in differentiating human sera. On a large number of cases it has been noted that agglutinins for OX-2 occur more frequently in the spotted fever cases than in the typhus cases, but since they do occur in endemic typhus the above finding is of no help in the individual case.

In patients the agglutinins for OX-19 usually appear toward the end of the second week of the disease. At times they are delayed until the cure of the illness or early convalescence. Some proven cases of spotted fever produce no agglutinins for Proteus X. The curve of agglutinin rise and fall is similar to that seen in typhus.

It has been reported that, following inoculation with spotted fever, rabbits produce agglutinins for both OX-19 and OX-2, while inoculation with endemic typhus is followed by production of OX-19 agglutinins only. Maxcy has suggested as a means of differentiating spotted fever from typhus that rabbits be inoculated with the blood of suspected cases and the production of agglutinins for these Proteus strains be observed.

Identification by animal inoculation

Spotted fever may be transferred from the patient to the guinea pig by intraperitoneal inoculation of whole blood or by the injection of the blood clot. The injected guinea pig develops a marked febrile reaction, which is followed by death in many instances. The fatality rate in guinea pigs varies from about 10 per cent to as high as 95 per cent with different strains. Com-

monly the strains isolated from cases in the eastern states have shown fatality rates up to 40 per cent, although at least one strain isolated in Virginia has killed over 80 per cent of the guinea pigs inoculated, which is similar to the rate seen in the Western strains of which we have records.

Scrotal reactions are produced in male guinea pigs by injection of some strains of spotted fever. The explanation for the lack of uniformity shown by strains is not clear; however, it may be bound up with the virulence or invasiveness of the strains, since the strains showing the higher fatality rates in guinea pigs also are more prone to cause scrotal reactions.

The scrotal reaction of spotted fever is unlike that of typhus. It begins as a macular rash on the skin of the scrotum about the 3rd or 4th day of fever. The macules rapidly coalesce and form dark purple areas which may include a large part of the scrotal skin, necrosis develops and is followed by sloughing and subsequent healing with scar formation. There is little edema of the subcutaneous tissues and the testicles can be readily pushed through the rings into the abdominal cavity, which is not true in the typical endemic typhus reaction.

Protection tests may be carried out on the serum of cases taken late in the disease or in convalescence. In these tests the suspected serum is mixed with the virus, in appropriate titration, and injected into guinea pigs. If protection is afforded by the serum this test is of great value, but sera from some recovered patients may show no demonstrable protection.

The histological changes in the brains of guinea pigs do not vary appreciably, as far as the character of the individual lesions is concerned, from the picture already described for typhus. Lillie has shown, however, that a higher proportion of the focal lesions is found in the midbrain, pons, medulla and cerebellum in spotted fever than in typhus.

Prevention

Methods for the control of spotted fever have been directed toward the eradication of ticks, but have not been very successful. The difficulties of the problem may be recognized when the vari-

ety of hosts on which these parasites may feed is considered. Poisoning of rodents, dipping of domestic stock, clearing away of brush and the burning over of tick infested areas all probably assist in the reduction of ticks, but it is only fair to state that, although such methods have been tried, there is little evidence that much has been accomplished in the way of limiting the disease.

Probably the most effective method of prevention is the exercise of personal care. Known infected areas should be avoided insofar as possible during the tick season. Those who must visit such areas should frequently examine their clothing and body for ticks. The tick usually does not become attached to its host at once but oftentimes crawls around for several hours. It has been shown also that the chance of receiving infection from the bite of an infected tick is directly proportional to the length of time the tick has fed on the exposed individual.

When removing ticks from the person or from pets care should be taken in handling the ticks. It is best to remove them with small forceps or with a piece of paper held in the fingers. The hands should, of course, be washed thoroughly with soap and water after handling ticks. Pets should be thoroughly deticked every few days during the tick season. There is little danger of leaving the mouth parts of the tick in the wound. The wound itself may be treated as any other abrasion, since there is nothing to distinguish the bite of an infected tick from that of a non-infected tick, nor is there any evidence that such measures as cauterization will lessen the chances of subsequent development of the disease.

Vaccine

A vaccine, for use against spotted fever, was elaborated by Spencer and Parker and is prepared by the U. S. Public Health Service at Hamilton, Montana. This vaccine is made from infected ticks and has been found of value in the prevention of the disease. Occasional cases occur among those who have been vaccinated, but such cases are usually mild. The evidence in regard to total prevention is hard to evaluate but seems to

indicate that it appreciably lessens the chance of contracting the disease. There is no good evidence that the vaccine is of value after the infection has been acquired, nor is it of any value in treatment.

It is not easy to decide the question of recommending or withholding the vaccine from any given individual. The methods of manufacture are such that the vaccine can not be produced in large enough quantities to provide for wholesale vaccination, nor is the incidence of the disease such as to warrant such a procedure. Vaccination is recommended for use only in those sections where the incidence of the disease and the fatality rate are high. In such areas vaccination should be reserved for those whose occupations or play expose them to ticks.

Proceedings of the Sections

SECTION ON GENERAL MEDICINE[1]

Regular Meeting, October 23, 1939

SEX HORMONE THERAPY OF MIGRAINE IN THE MALE. Charles William Dunn, M.D. (*Abstract below.*)

CHEST ROENTGENOGRAMS IN POLYCYTHEMIA VERA AND POLYCYTHEMIA SECONDARY TO PULMONARY ARTERIOLOSCLEROSIS.[2] Philip J. Hodes, M.D., and John Q. Griffith, Jr.,[3] M.D. (*Abstract below.*)

AN EVALUATION OF THE BLOOD BANK. William P. Belk, M.D., and (by invitation) Norman W. Henry, M.D.

REPORT OF THREE CASES OF "CLINICAL" ADDISON'S DISEASE IN WHICH THE PATIENTS SURVIVED MORE THAN FIFTEEN YEARS.[4] L. G. Rowntree, M.D. (*Abstract below.*)

Abstracts

SEX HORMONE THERAPY OF MIGRAINE IN THE MALE. Charles William Dunn, M.D.

The report concerns the use of testosterone propionate and oestradiol benzoate in males with migraine.

Oestradiol benzoate in dosage from 2,000 R. U. aborts a migraine attack if administered at the onset of the attack. A short series of injections of 5,000 R. U. of oestradiol benzoate prevents the recurrence of the attacks for as long as three months in cases subject to frequent migraine attacks.

A full therapeutic dose of testosterone propionate, 25 mg., does not relieve or influence a migraine attack in males. It benefits them constitutionally if hypogonadism is present.

[1] *Chairman*, J. Alexander Clarke, Jr., M.D.; *Clerk*, Thomas Fitz-Hugh, Jr., M.D.

[2] From the Department of Radiology, the Robinette Foundation, and the Medical Clinic of the Hospital, of the University of Pennsylvania.

[3] A. Atwater Kent Fellow in Clinical Medicine, University of Pennsylvania.

[4] From the Mayo Clinic, Rochester, Minnesota, and the Philadelphia Institute for Medical Research in the Philadelphia General Hospital.

From an endocrine aspect, the cases studied were mild types of anterior pituitary deficiency with secondary hypothyroidism being more prominent than hypogonadism.

The continued administration of estrogenic substance in dosage above 2,000 R. U. produces in some patients gynecomastia. Histological investigation of the removed breast tissue reveals that it is the typical estrogenic effect of estrogenic substances on the breast tissue, and is of a benign character. The induced estrogenic gynecomastia undergoes resolution in about six weeks.

Chest Roentgenograms in Polycythemia Vera and Polycythemia Secondary to Pulmonary Arteriolosclerosis.
Philip J. Hodes, M.D. and John Q. Griffith, Jr., M.D.

The chest roentgenograms of 11 patients with polycythemia vera and of 3 patients with polycythemia secondary to pulmonary arteriolosclerosis have been reviewed in an effort to determine whether there exist roentgenographic differences between the two conditions.

Eight of the 11 patients with polycythemia vera presented marked increase in prominence of the truncal shadows of the lungs. In addition, 3 patients presented circumscribed nodular lesions in the chest roentgenograms which have been attributed to stasis infarction.

The chests of the patients with polycythemia secondary to pulmonary arteriolosclerosis did not reveal the changes described above. Instead, marked prominence of the hila, increased prominence of the pulmonary conus, and hypertrophy of the right heart were presented.

Report of Three Cases of "Clinical" Addison's Disease in Which the Patients Survived More than Fifteen Years.
L. G. Rowntree, M.D.

These case reports are not presented with the thought of emphasizing the effectiveness of the Muirhead regime, which was employed, but rather to indicate the actual survival of occasional mild cases under older methods of management.

In the first case, due to tuberculosis, the patient succumbed after 18 years, the general tuberculosis playing a rôle in the fatal outcome, the local tuberculosis lesions constituting the destructive factor in the suprarenal glands. In the second case, due possibly to lues or tuberculosis, one or both, the patient is still alive after having suffered for 15 years from a mild form of Addison's disease. In the third case, idiopathic in origin and probably functional in character, the patient has been almost completely well for the last 12 years; and hence probably represents an arrested case of Addison's disease which started some 17 years ago. These three cases represent the longest survival-time in the 116 cases discussed in 1931 in our book on Addison's disease.

SECTION ON MEDICAL HISTORY[5]

Regular Meeting, October 9, 1939

An Account of the First Colored Practitioners of Medicine in the United States. Harold Farmer,[6] M.D.

Origin of the 15th-Century Epidemic of Syphilis. Franklin H. Church,[6] M.D.

Human Credulity as Illustrated by Witchcraft. Theodore Diller,[6] M.D.

SECTION ON OPHTHALMOLOGY[7]

Special Meeting, September 28, 1939

Special Relationships between the Hypophysis and the Eye. Josef Igersheimer,[8] M.D.

Regular Meeting, October 26, 1939

Report of a Case of Rhinosporidiosis of the Conjunctiva. Harold D. Barnshaw, M.D., and William T. Read, Jr.,[8] M.D.

Report of Cases of Diplopia Following Fracture of the

[5] *Chairman*, Burton Chance, M.D.; *Clerk*, Louis B. Laplace, M.D.

[6] *By invitation.*

[7] *Chairman*, Alexander G. Fewell, M.D.; *Clerk*, Warren S. Reese, M.D.

The proceedings of this Section are abstracted in the *American Journal of Ophthalmology* and the *Archives of Ophthalmology*.

[8] *By invitation.*

Malar Bone. H. Maxwell Langdon, M.D., and Robert H. Ivy,[8] M.D.

Management of Some Cataract Surgery Complications. Edmund B. Spaeth, M.D.

Clinical and Experimental Studies of Interstitial Keratitis. Joseph V. Klauder,[8] M.D., Elmer R. Gross,[8] M.D., and Harold F. Robertson,[8] M.D.

SECTION ON OTOLARYNGOLOGY[9]

Regular Meeting, October 18, 1939

Acoustic Tumors. Walter E. Dandy,[10] M.D.

SECTION ON PUBLIC HEALTH, PREVENTIVE AND INDUSTRIAL MEDICINE[11]

Meeting, October 30, 1939

Medical Service Plans: a Consideration of the Principles Involved. Francis F. Borzell, M.D.

The Medical Service Association of Pennsylvania: a Voluntary Insurance Plan for Furnishing Medical Service to Low-Income Groups. C. L. Palmer,[12] M.D.

[9] *Chairman*, Warren B. Davis, M.D.; *Clerk*, William Hewson, M.D.
The proceedings of this Section are abstracted in the *Archives of Otolaryngology*.
[10] *By invitation.*
[11] *Chairman*, Maurice S. Jacobs, M.D.; *Clerk*, J. H. Arnett, M.D.
[12] *By invitation.*

The Legacy of Rome in the History of Medicine*

By Arturo Castiglioni, M.D.

I

In a brilliant period of Italian history, that of the Renaissance, Rome was looked upon as the master in the arts of war and of the law, as the conqueror and dominator of peoples; and when the Italians, with an outburst of faith and will, tried to relate their strong yearnings to the traditions of their forefathers, every beautiful and wonderful thing in the world seemed to them to have belonged to Rome. What Greece had accomplished in the field of thought seemed almost forgotten. Romans were then regarded as insuperable masters not only in war and politics, but also in the fields of science, letters and art.

That was the time when Celsus was regarded as the best of physicians and Pliny was read and studied with the care owed to a classical text, while these and other Latin writers were believed to be the greatest authorities in the field of medicine.

Later, when historical criticism began to take shape, when the Greek texts were discovered and studied with great devotion, opinion veered to the opposite extreme. Many historians have declared, and still declare, that to the field of science Rome brought a very small contribution, that everything accomplished in Rome in the medical field was Greek, because the Romans were in medicine, as well as in art, the more or less successful and faithful, even servile, imitators of Greek genius.

From an exaggerated admiration we passed, thus, to an excess of depreciation. Today, however, we are able to consider the importance of Latin thought in the history of science, and above all in medical history, from an entirely critical and objective point of view.

* Read at a joint meeting of the Section on Medical History and the Friends of the Library, The College of Physicians of Philadelphia, November 13, 1939.

II

In the first stage of Roman civilization, Latin thought followed the direction traced by Hellas. But in history—modern research has made this clear—there are no sudden beginnings of civilizations, as was formerly believed and taught. Today, we know that the period regarded by us as the golden age of Greek culture, that the Athens of great philosophers, orators, and artists, was in reality the renaissance of a much more ancient and highly developed culture which had had its home in the Aegean islands. Thus, in a thousand ways and through a thousand currents are obtained those cultural results which seem completely original to the future observer, but which are, in reality, and so appear to the eye of the critic, the result of many factors come from unknown, and sometimes forgotten, origins.

Greek culture, in its Hellenic splendor, was that wonderful phenomenon which was brought about when, together with trade from the Aegean islands, there came to Hellas currents of thought, of method, of ideas, and of critical experience. Under an always brilliant sunshine, thousands of ideas and tendencies of thought met, and the critical power of men of really high feelings and deep analytical sense determined a definitive direction for the history of human thought and art.

Rome inherited this direction from Greece. We forget too often, and I think it right to recall it, considering the importance the fact has in the history of medicine, also, that there was always an intellectual intercourse between Italy and Greece, even in the most brilliant moment of Hellenic culture, and many well known doctrines of the classic Greek philosophy and of that medicine which we are accustomed to call Hippocratic, came from that school called by Aristotle the *Italic* school—the school of Pythagoras, which found its right setting in southern Italy.

By this school was formulated for the first time, and for all time, the fundamental concept of the mathematical law of nature, the thought of the law of numbers, which, it is historically important to note, was proclaimed again, twenty centuries later, in Galileo's words: "Nature is written in mathematical figures." This fundamental concept, which lasts through centuries in the

history of Latin thought, constitutes its most characteristic aspect. Latin thought is critical and orderly: it defines and states right proportions.

The medicine of Rome was also Latin in tradition, because it first absorbed and consolidated the teachings of the peoples with whom the young state came in contact.

This ancient tradition was not to be discarded. We know that the Etruscans had, already in ancient times, the fame of excellent physicians. Homer had already told that the sons of Circe, who knew how to mix poisonous and wonderful healing substances, became princes of Etruria. In Etruscan tombs have been found gold teeth in the jaws of skulls, demonstrating that the dental art had reached a high stage of development among the Etrurians. We know that in Etruria extremely important projects for the drainage of the ground had been carried out; there are still standing some galleries built in an attempt to dry up the marshes and thus prevent an impending outbreak of malaria. And, if tradition attributes to Tarquin the Proud, the last Roman king, the building of the *Cloaca Maxima* (one of the most wonderful works of hygienic importance in ancient times), it is obvious that such a hygienic measure, so largely conceived, had already been imagined or prepared by the ancient Etruscans. It would be inconceivable, otherwise, for a king of Etruscan origin to carry through such a monumental work only a few centuries after the foundation of the city.

Roman medicine breaks away rapidly from the mythological tradition. By this we do not mean that the people abandoned superstition and the magical concept—which no people has really been able to give up completely. That profound universal concept seems, in fact, to be as old as mankind and not destined to disappear. The magical concept continued to be an outstanding feature in medicine, but it is difficult to say whether it was more powerful in ancient Rome than it is in the world of today. However, we see that one of the most ancient Roman laws forbids medical practice by magicians and haruspices, and establishes the civil responsibility of the physician toward the patient.

In the later times of the Republic, we find legislation in the

matter of hygiene that is highly perfected: rules to settle the physical education and to control the welfare of children; preventive measures against epidemic diseases; the appointment of ediles to supervise the market-place; a law defining the functions of the magistrates charged with inspecting the water; all the wonderful provisions to ensure a pure water supply which enabled Rome, within a few centuries, to provide the people with more wholesome drinking water than any they have had up to the present time. Good examples of such provisions are the eleven aqueducts, one of which, the famous Marcian aqueduct, cost a sum equal to about $150,000—which indicates how much Rome spent for the health of its inhabitants.

We see, also, the admirable way in which the big public baths were built, with their luxurious accommodations, including halls for all kinds of exercise. There is no cultured physician who cannot find in the recollection of his studies or of what he has actually seen, a more or less correct picture of these buildings. I believe, however, that the actual construction of these baths is less important, historically, than the circumstance that in those days there could have been conceived constructions so monumental in plan and so perfect in detail that we, today, with our concepts of great capitols and their needs, would regard one of them as being extravagant for a city with a population ten times greater than that of Rome in those days. This is the Latin grandeur, which built *sub specie aeternitatis*, like the Italy of the Renaissance, which set out to crowd streets and squares with statues and cathedrals.

Together with these sanitary measures, Rome instituted State administration of public health; and it is in Rome that, for the first time, the physician appointed to a public function is considered a State official.

It is known that in Rome, during the Republic, only foreign, and especially Greek, physicians practiced medicine; and that, when the stern censors began to fear that the Greeks might bring corruption to Rome, the Greek physicians residing in the capitol were severely judged.

We must say that this attitude was not entirely unjustified,

because, certainly during the period of the Republic, there came to Rome and professed the medical art many individuals who had only the self-given name of physician and who knew very little about medicine. Often they were slaves or freedmen who under the name of medicine practiced many disreputable and often ignominious arts.

When Cato wrote to his son, "Beware of physicians; avoid them as the greatest danger above all, the Greeks, who are dangerous men," he was not entirely wrong. We know that there was some reason for his feeling. Little by little, however, things took on another aspect. When Asclepiades, a man of great intelligence and a skilful practitioner, began to practice in Rome, many studious and scholarly physicians had already realized how much there was to be done, and how many possibilities were offered by this great city. Greek doctors, coming from the schools of Athens and Alexandria, won the confidence of the most eminent people and became friends of the great politicians; and when, in the year 46, Julius Caesar bestowed Roman citizenship on physicians, a new era began for them. We may say that this event marked the beginning of a new epoch in the history of Roman medicine, because, with the granting of this right, the dictator proclaimed that the physician, as such, had the right to that title which otherwise was obtained only through nobility or wealth, or by having been born in Rome. It was, therefore, no longer dishonorable for a Roman citizen to practice medicine.

Physicians owe also an additional debt to Caesar, because the great leader and the great writer rightly appreciated the part a physician might play in a state governed by truly political (in the widest sense of the word) concepts.

III

The most striking figure in the history of Roman culture is Lucretius, the poet, near to Vergil in his high concept of poetry and in the glorious beauty of his verse, a philosopher who sees limpidly with his clear eyes beyond the frontiers of time and space. Lucretius, wrote an American historian, thought to rise with Epicurus beyond the flaming ramparts of the world and by the living force of his soul to win a victory over ignorance. He

was a Latin scientist, a sound philosopher, but also an ardent lover of beauty, a profound and severe critic, but at the same time the creator of a new world, to which only a critical judgment joined to a passionate love of art can be the guide.

The atomistic doctrine, which is the basis of modern chemistry, the law of the conservation of energy, the theory of the evolution of species, the law of the cycles, the accentuation of the cosmos as the center and essential part of life—all these doctrines are found in Lucretius, and found based on observation and reasoning. Therefore, his poem seems really to be the most perfect proof of the grandeur of what could be called the Latin renaissance of Greek thought.

But in the golden age of Latin literature some great Latin writers were already beginning to deal with the subject of medicine. We may cite here two of the more famous ones: Aulus Cornelius Celsus and the elder Pliny. If we consider, even rapidly, the work of these writers, I believe that we may easily recognize the existence in their works of that fundamental concept which I consider essentially characteristic of Latin thought.

Aulus Cornelius Celsus is an encyclopedist; he has surely a profound knowledge of medicine but does not engage in medical practice; he is a scholar who collects and selects the results of his studies and observations. To Celsus we owe our knowledge of ancient medicine and of its history. With the careful method of the scholar and the observer he orders his material, and for the first time in history writes a scientific book which is a medical treatise systematically conceived. Diseases are divided according to their treatment, diet, remedies, and surgical intervention. This crude method of division is open to discussion, but at any rate it marks the beginning of a system and shows the necessity of bringing order into the very concept of disease. Celsus is essentially Roman: he brings together, and orders, the most complex and scattered material drawn from his observations.

Pliny the elder deserves a deeper study than is usually made of him. He came of a noble family; had high charges from the Republic; loved study and deep research; and was, at one time, at the head of the navy.

When streams of lava were already breaking out from Vesuvius,

Pliny, well aware of the danger but realizing the importance of the phenomenon, wanted to observe it at close range. Herein we see the critical spirit of a Latin scientist, without whom, it seems, not even an eruption of Vesuvius could take place, because he must witness it, follow the development of the tragedy, and write his account of it. In the eruption of Vesuvius the great naturalist finds death and, together with death, fame. But in his book he has related with an extraordinary patience and exactitude all the knowledge of his times; not only all the results of research and of his own practical experience, but also the superstitions and popular beliefs current in his time.

In his book of natural history Pliny discusses all the most remarkable phenomena of life and death. He writes of diseases and their cures, of strange animals and magic plants; but he also collects many precious personal observations, and thus composes an encyclopedic work — the most wonderful work handed down to us from ancient times. Of course we cannot judge the work from the point of view of a modern encyclopedia: obviously, when we read tales about the virtues of some plants or about the prophylactic method of preventing some disease, we are inclined to smile, because we think "these are superstitions and errors." But apart from the fact that in every error there is always a grain of truth (it would be enough to cite the discovery of the use of atropine in ophthalmiatria), this vast work is extremely important for us in that it gives us an idea of the method of Latin thought. This I take to be of great value. We shall never get a just appreciation of an individual if we merely cite the mistakes in one of his actions or thoughts; it is the method of his reasoning that we are obliged to study and understand. Latin reasoning is constructed, we may say, on foundations as solid as those on which Latin architecture is built.

Only a superficial observer, and a not very conscientious judge, can accept the possibility of reconstructing the history of medicine in single parts, without regard for the history of civilization as a whole. In the same way, the physician who proposes to relate the history of one of his cases without referring to the heredity and the environment of the patient is not a thoroughly con-

scientious physician. If we consider the evolution of Roman thought in letters, in law and in the arts, we find everywhere this characteristic of comprehensiveness, this tendency to systematic arrangement, this inevitable urge towards a critical and mathematical order of things, the need of defining the limits of men's functions, and, finally, the deep judicial analysis, the clear synthesis in conclusions.

IV

Are we, then, in a position to state that Latin medicine brought a contribution to the history of science? I am inclined to say 'yes'—or, rather, I think that we may say that it was indeed Latin mentality which brought system and order into the study of medicine, and that it was Latin medicine which gave a new value, and a definite function in the state, to the physician's profession. In fact, the Romans, men of war and conquerors, were the first to establish military medicine on a strong basis. Every cohort and every trireme had its surgeon, and only the surgeon had the right to be compensated by the state for what he had lost during his military service. The surgeon enjoyed all privileges under the law; he was a citizen, and, above all, he was always, even when he was not filling a special charge, a state official—from the palatine archiatres, who were the highest medical officials, down to the village physicians, who were also under the control of the authorities, because only a physician who had passed the prescribed examinations had the right to practice his profession under the protection of the state.

Therefore, Rome, being a military state, introduced and encouraged the organization of military medicine; the state which laid the basis of civil legislation defined the physician's status in the eye of the law. Rome created legal medicine, and stated with definite rules the physician's functions and rights before the tribunals; but at the same time (and this shows the wisdom of Roman law) it did not forget to state his duties and his penal and civil responsibilities. In line with these functions, Rome was the first state to provide physicians with a suitable education, and already under Septimius Severus we get evidence of well organized

schools with their special libraries, while there was even a law ordering that pupils showing no sense of discipline be expelled from the school, after first having been publicly warned.

Thus we see that, in spite of the belief that Rome did not produce anything really new in the field of scientific medicine, we must at any rate thank her for having founded and organized the systemization of medicine, for having created state hygiene and social medicine.

Is the common belief that scientific medicine shows no progress in Roman history really true? Rome had inherited, first Greek, and afterwards Hellenistic, culture. In Alexandria, anatomy and physiology had already seen some important discoveries; the schools of Herophilus and Erasistratus had already initiated interesting physiological studies; in many fields the beginning of a new era was already appearing, when suddenly, with the fall of Alexandria, the studies were abandoned. One must bear in mind the political situation of the moment. Rome was surrounded by powerful foes and had first to attend to the formation of what was to be the source of its power later on—the solid basis of the state and the legislation. We are well aware that scientific research (history shows this by a hundred examples) can take place only in a period of economic welfare, during a period of peace, having no means of flourishing when a country is upset by war and rebellion.

In the first period of the Republic, troubled by wars, Rome, before succeeding in dominating all enemies far and near, is completely occupied by the problem of empire; only when the empire is solidly built, does Rome turn her attention to science. Then, it is in Rome that one of the most famous physicians of history appears—Galen, a great master, who was born in Asia Minor and wrote in Greek. Greek was, in fact, the scientific language and Latin was not willingly used for scientific purposes.

The book was Greek, but Galen was representative of scientific thought in Rome. His mind, however, was Latin, because it was, above all, critically systematical. Galen's most important achievement was to have gathered and collected facts, enclosing them in a wonderful system, most originally conceived, with an inspired vision which, today, after eighteen centuries, arouses

our deepest admiration for the work of this physician and writer, Greek by birth, but Latin in thought, who spent all his life in Rome, felt Rome's influence, and created this school under the spell of Latin culture.

After this period, Latin medicine shows signs of decadence. The city, which had so wonderfully built its own greatness and seen to the health of its citizens, declines. There is a cause of this decline which is, to my mind, most important and interesting, though it has been very lightly touched upon by historians: the chief cause of Roman decadence was not the corruption of manners, but the great plagues which ravaged the peninsula, each one carrying off many thousands. Whole towns, whole regions were laid waste by death, and the Italian population was reduced to one-tenth its size by this dreadful calamity.

Afterwards, with the coming of Christianity, we have a new bearing in medicine, resting on the concept of healing faith, of cures by divine intervention. With the idea of the vanity of scientific research brought about by Christianity, which conceives medicine as a work of charity, medicine becomes spiritual and evangelical.

V

But where do we find a renewed expression of critical, synthetical thought in medicine? Latin thought now becomes Mediterranean thought, feeling the currents of the Arabian culture, the influence of Oriental art.

The Mediterranean is the theatre of all battles and of all wars; of all trade rivalries, of all conflicts of thought. The shores of this sea have been bathed in blood for centuries, and they have seen the dawn of the three most important religions of humanity. On these shores have shone the leading lights of civilization: from the ancient schools of Nineveh and Babylon to the schools of Athens and Cos; from the Alexandrian to the Arabian schools; from Byzantium to Marseilles; from the Sicilian schools to the schools of Salerno, Venice, Pisa, the Mediterranean sea has been the stage of the fiercest battles, but also of the most brilliant intellectual victories.

Latin medicine becomes Mediterranean medicine, and on the

Italian shores, at Salerno, rises once more one of the greatest schools—the first lay Latin medical school.

It has been wrongly thought that Salerno was a Greek or Arabian school. Salerno was a Latin school, because in it were revived the Latin teachings which had been kept in the cloisters during the so-called Dark Ages, during which these traditions had never been lost, because the lamp burning in the monk's cell was the only light which kept the torch of Latinity aglow through centuries. Salerno was a Latin school, also, because all the Salernitan teaching had the characteristics of Latin thought: Salerno was a practical school, in which we find teaching once more perfectly organized. Its Latin origin is shown, also, by the fact that, for the first and perhaps the last time in history, a medical school expresses its teaching in Latin verse and publishes that *Regimen sanitatis* which, after Hippocrates' *Aphorisms*, was for centuries the most read and studied medical work, being translated into all languages the world over. In this work are collected, in a thousand lines or so, important diagnostic, therapeutic, and hygienic formulas. It is, then, at Salerno that we find once more the current of thought and of practical teaching which we shall trace later in the Italian schools of Padua and Bologna, which became centers of learning. At Bologna the study of anatomy begins in the 14th century.

VI

No other country was so ready as was Italy for the discovery of anatomy; in no other country had there appeared that yearning for research which had the power of proclaiming once more, after centuries of silence, the faith in life and science. This faith manifested itself in the Italian universities of the 14th century, notably when the center of anatomical studies throughout the civilized world was created in Bologna and, later, in Padua, whose university the great Swiss scientist Haller was able to call the master university in all Europe for a century and a half.

The Italian Renaissance marked an historical epoch, and it is quite clear (this is not a new statement) that the return of

humanism brought back again to the Italian people the Latin tradition—and with it, the consciousness of duty, suggested by historical tradition, and the love of glory. This love of glory is the new manifestation of the faith in immortality—the eternal faith in the rebirth of the individual, which is as old as humanity and can be traced in the histories of the earliest peoples about whom we know anything. In Renaissance Italy this element takes on a new aspect—becomes love of immortality, of fame, of glory, and of beauty, admiration for the beauty of the human form, love of art. The individualism revives, in a new shape. It is typically Italian that through the love of art there should arise in Italy the love of anatomy, and that Leonardo da Vinci, the greatest of artists, the greatest of thinkers, in whom are wonderfully united all the most precious and productive faculties of genius, should have been the founder and leader of anatomical studies. Leonardo did not believe in Galen's authority, did not follow ancient masters, did not study anatomy in books, but was able, nevertheless, to investigate the deepest problems of human existence and see with clear, mortal eyes beyond time and space; he was able to foresee the new trends of science, and, being at the same time a great technician and a great artist, a philosopher and a poet, he saw and understood the necessity of solving the problem of life, writing as a program for his anatomical studies these splendid, proud words: "I shall discover unto men the first, or perhaps the second, cause of their being."

If we examine Leonardo's manuscripts and sketchbooks, we see today, four hundred years after the execution of these drawings, that they form the most perfect book of anatomy that ever existed. There has never since been the case of a great anatomist who was also the greatest artist of his times, of a deep observer who had also a passion for anatomy.

Leonardo shows by his unique example that a man of science may be an artist, and that a good critic may be a man of science. In the Renaissance, this is perhaps the characteristic of Latin thought, the characteristic of the universal man, of whom we have so many wonderful examples; a man who, with the same enthu-

siasm and skill, could consider artistic as well as political and scientific problems, write verses as well as go deep into anatomical questions; who is a master in all fields of technique.

VII

I have rapidly sketched a picture of the evolution of Latin thought and of the legacy of Rome in medicine, and I come now to a conclusion.

There was a period—50 years ago—in the history of medicine, in which a materialistic concept was predominant, and in which no problem seemed impossible of solution in the laboratories. The general opinion was that the physician should be, above all, a scientist, and that all problems might be solved with instruments and formulas. This was the time when one of the most celebrated of German scientists wrote that the clinic is only the ante-room to the laboratory. Today, medicine has taken quite another direction, together with the movement which we might call neo-classical in the fields of chemistry, physics, and others of the exact sciences. We have come to the conviction that few of the problems of life are explained today, and that about the essential human vital function we know as little now as we did in the remote past. We are aware today that all the microbiological problems, though they have been wonderfully discovered and solved, have not cleared up any of the questions that we supposed might be decided through them, some even having thought that microbes were the cause of all disease. We are now at a decisive turn in the history of medicine—so decisive that in some countries, in Germany, for instance, everyone speaks of a crisis in medicine; and this expression "crisis in medicine" has become the password in all Anglo-Saxon countries, though we may say that this "crisis" is much less felt in the Latin countries.

Latin thought, in its true tradition, is measured and synthetical, and it allows a great part to the patient's personality. It is not only by chance that the Italian school of constitutional pathology inherited the old Hippocratic doctrine. The constitutional doctrine has prospered in Italy because there the comprehension

of the value of personality has never been completely overshadowed by the concept of the omnipotence of laboratory research. But that does not mean that we believe that laboratory researches are an actual failure. This might be said only by one unaware of the most wonderful work of scientific discovery in the last twenty or forty years. I say merely that the doctor of today has reached a balanced judgment, a biological bearing, a concept which prevents us from considering the physician only as a scientist looking for the solution of problems in the laboratory, teaching us that he must be also an artist who judges with broad mind and critical reasoning. The conclusions, the subjective understanding of personality which a reasoning, enlightened man finds in personal experience are the only means from which he may derive a judgment of benefit to the patient.

Latin thought, which has been essentially balanced and critical, has, therefore, had this pre-eminent characteristic from the first hygienic rules of the small town to the modern measures for malaria prevention and the protection of the welfare of mothers and children. It has given a right appreciation of values through centuries; and if we regard this as a Roman inheritance and tradition, we might say that the work of a state which has seen in such a wonderful way to the health of its inhabitants —which has, within its laws, the implication that the health and welfare of the citizens is a necessary factor in national greatness— cannot be charged with having brought no contribution of importance to the history of medicine. Through many ways and endless struggles, during long periods characterized by economic and civil wars, across the sea disputed with arms in the conflict of different interests, the Latin concept has affirmed and proved its historical importance.

If we consider with a clear and impartial mind the legacy of Rome to the history of medicine, we must rightly conclude that no one could possibly overlook it without disregarding one of the great sources that definitely helped the formation of contemporary medical thought.

A Resurrection of "Pile"*

The Peter A. Browne Collection of Hair in the Mütter Museum

By Joseph McFarland, M.D.

Curator of the Mütter Museum of The College of Physicians of Philadelphia, Fellow of The College of Physicians of Philadelphia

It seems to be generally accepted that "rolling stones gather no moss," and, conversely, that fixity of position and purpose afford the greatest opportunity for it. Of the members of a community, few find firm anchorage more necessary than the doctors, to whom a change from one place to another may mean the loss of a practice laboriously gained, and the acquisition of another only through added years of toil. Doctors are, therefore, apt to be fairly permanent members of those neighborhoods in which they practice, and many spend the greater part of their lives in the same city, the same district, and, sometimes, in the same house. The "moss" that accumulates as the result of this habit is not all in the form of real estate, bonds, stocks, and cash in the bank; much of it is in the form of books, instruments, specimens, case histories, indices, reprints and other miscellany, often of surpassing interest to the collector, but bewildering to any other not of the same ilk. It is, therefore, little wonder that, when a doctor dies and the members of his family or clan gather to divide his "moss," they encounter a multitude of strange and incomprehensible things devoid of personal sentiment, of no commercial value, and frequently of repulsive or even shocking appearance, the disposal of which is perplexing and perhaps embarrassing. Under such circumstances, after deliberation and interrogation, it is decided to get rid of the mess by presenting it to "The College of Physicians," and one day a car drives up to its front door, or a truck to its back door, and the cargo is deposited in the College basement.

* Read before The College of Physicians of Philadelphia, the Section on Medical History, May 8, 1939.

It was in an accumulation of this sort that there was found that which prompted the writing of this paper, the "Peter A. Browne Collection of Pile."

The matter might have been dropped as of little moment, had not the sight of this collection revived certain memories of boyhood days and a gruesome and thrilling detective story in which a man was arraigned for murdering a neighbor against whom he was known to have long nursed a desire to avenge an injury. The damaging evidence was in the form of a knife with which the murder was supposed to have been committed, and upon the blade of which clotted blood and certain hairs were found. The accused declared his innocence, and explained that he had been sitting in the woodshed, whittling a piece of wood, when a large rat popped out of a hole close at hand. He made a sweep with the knife, struck the rat, almost cutting it in half, when the dinner bell rang and he laid down the knife and the wood, intending to return to them later. An expert to whom the knife had been subjected, and who knew nothing of the defendant's story, reported the hairs upon the knife to be "from the back of a Norway rat," the jury was convinced that the accused was innocent and he was acquitted.

It was not long after reading that story that hairs were being collected from the heads and beards of all the family, from cats, dogs, horses, cows, rats and mice, and that later an excursion was made to the Zoölogical Garden, where a keeper of animals was finally cajoled into contributing a few hairs pulled from an indignant lion, an angry tiger, a vicious and vindictive leopard, and some other wild animals. All of these were carried home in triumph and having been prepared with such care as a youth might be expected to exert, were examined under a cheap microscope. The results were most disappointing; it did not seem possible to identify each animal by its hair and all were subsequently thrown away. However, one thing came out; the report in the story was based upon fact, for the hairs of the rat and those of a good many other animals can very easily be differentiated from those of a man, though not always from one another.

So interest in this newly found collection of hair was inevitable. It was an object of unprepossessing appearance, a kind of

extemporized portfolio made from the torn-off cover of an old copy book, filled with sheets of paper a little too large to fit, and consequently projecting irregularly at the top and bottom edges. It was covered with the dust of ages, and was so fragile as to threaten to crumble when handled. Pasted upon the outside of the cover were three labels that read:

> A Collection of Specimens of Hair representing different nationalities and different diseases. Mounted and described by P. A. Browne, LL.D. 1851. Presented by Dr. S. Weir Mitchell.
>
> HAIR
> 1800
> Presented by Dr. S. Weir Mitchell.
>
> A Collection of Specimens of Hair Representing Different Nationalities and Different Diseases.
> Mounted and Described by P. A. Browne, LL.D.
> Presented by Dr. S. Weir Mitchell.

The first of these labels was printed, and appears to have been cut from a College of Physicians Program, presumably of the date 1851. It was, however, impossible to confirm this supposition, for the College possesses no collection of the program announcements of that period. But the breadth of the page, and the size and style of the printing conform with those of a somewhat later date. The second label was hand-written, the third printed with a pen upon a fragment cut from a filing card. All were probably affixed by former curators of the museum.

Inside the portfolio there are forty-six sheets of yellow-brown paper and one of white paper ten inches long and six inches wide, and thirty-nine sheets of pale blue, lined note-paper eight by ten inches and stamped "Carew Co." in the corner.

With the exception of three, to which reference will be made later, each sheet has a specimen of hair—sometimes a tress, sometimes a lock, sometimes a few single hairs—painstakingly affixed to it by small bands of gummed paper, or by a bit of court plaster or adhesive plaster. At the top of each is written "P. A. Browne's Collection of Pile," while at the upper right upon each of the blue sheets is written "Collected and Prepared by P. A. Browne" or "Prepared and Examined by P. A. Browne." The

upper left corner is usually reserved for the name of the donor of the specimen, and we read "Presented by Prof. J. K. Mitchell"; "Collected by Dr. William Pepper"; "Collected by Dr. D. J. Cain of Charleston S. C." Twenty-three specimens are credited to Dr. William Pepper, one to Prof. J. K. Mitchell, one to Robert King Stone, Washington, D. C., one to Dr. Henry R. Trout, Charleston, S. C. Some without such acknowledgments were probably collected by Browne, himself. They are from the heads of Indians, from the head and beard of a woman 103 years old, and one is "hair grown after death."

In almost every case, the specimen of hair is protected by a fly leaf of thin paper. Two of the yellow sheets had each several wood-cuts, looking like the proofs of cuts made for a book, cut out and pasted on. One of these pictured hairs of a "Plica Polonica," the other "Hair in Tinea Capitis."

The white sheet seems to have been that upon which Browne displayed the superlative degree of his skill as a preparateur: across its top is written "P. A. Browne Collection of Pile." A frame for the specimens to be exhibited has been prepared by cutting from some illustrated book or paper a representation of a Greek window frame of the Doric order, base, column and capital on each side, lintel with cornice surmounted by tympanum above, sill and dado between the bases below—and pasting it upon the sheet. In the tympanum an additional narrow slip of paper has been pasted, bearing the inscription "Ducit amor patriae"; just below the lintel another slip, pasted on, bears the words: "This is the finest wool ever grown on a sheep." Below this are two rows of four clippings each of brownish white fleece, each fastened by a slender red string that penetrates the paper on each side and is included in the paste behind it. At the bottom, the dado is filled in with a rectangle of paper on which is written: "Wm. Hall, Allegheny Co. Penn."

The actual contents may be indexed thus:

CONTENTS OF THE PORTFOLIO

Animal Hair (P. A. Browne's collection of Pile)

1. Hair of a common goat
2. Fleece of a ¼ blood Cashmere kid

3. Fleece of a ¾ blood Cashmere kid
4. Fleece of a full blood Cashmere goat 4 years old
5. The finest wool that ever was grown on a sheep

Human Hair (Collected and prepared by P. A. Browne)

6. Cylindrical Hair—Head of Bish-a-ki-se-guan. Algonquin Indian
7. Cylindrical Hair—Head of young Black Hawk—Algonquin
8. Cylindrical Hair—Head of a Mestizo—Half Indian and half white
9. Pure Concentrically Elliptical Hair—Wool of African Negro
10. Oval Hair
11. Oval Hair—Female

Curios

12. Plica Polonica—Notes 12 B—Presented by Prof. J. K. Mitchell (1 page of notes)
13. Hair of four pregnant women—Collected by Dr. William Pepper
14. Hair—Head and Pubis of the Man-Boy—Presented by Robert King Stone, Washington, D. C.
15. [Lost.]
16. Hair that came from the uterus of a "Mulattin"—collected and prepared by P. A. Browne
17. Hair of a white Albino—Collected and prepared by P. A. Browne
18. Hair of the aged—woman aged 103 years. Some hair also from her beard—Prepared and examined by P. A. Browne
19. Hairs grown after death—Collected and prepared by P. A. Browne
20. New growth of hair at 89 years of age

Disease Specimens

21. Neuralgic—Collected by Dr. William Pepper
22. Jaundice—Collected, Prepared and Examined by P. A. Browne
23. Albuminuria—Collected by Dr. William Pepper
24. Albuminuria—Collected by Dr. William Pepper
25. Anemia—Collected by Dr. William Pepper
26. Amenorrhoea—Collected by Dr. William Pepper
27. Typhoid Fever—Collected by Dr. William Pepper
28. Typhoid Fever—Collected by Dr. William Pepper
29. Intermittent Fever—Collected by Dr. William Pepper
30. Intermittent Fever—Collected by Dr. William Pepper
31. African Fever—Collected by Dr. William Pepper
32. Rheumatism (acute)—Collected by Dr. William Pepper
33. Aortic Rheumatism—Collected by Dr. William Pepper
34. Chronic Bronchitis—Collected by Dr. William Pepper
35. Chronic Pleurisy with Large Effusion—Collected by Dr. William Pepper

36. Phthisis—Collected by Dr. William Pepper
37. Phthisis, advanced with cavities—Collected by Dr. William Pepper
38. Phthisis, advanced with cavities—Collected by Dr. William Pepper
39. Scrofula with Caries—Collected by Dr. William Pepper
40. Scrofula—Collected by Dr. William Pepper
41. Coxalgia (2 extra pages of notes follow)—Collected by Dr. William Pepper
42. Syphilis—Babe 4 months old—Collected by Dr. William Pepper
43. Syphilis, secondary with ulcers—Collected by Dr. William Pepper
44. Syphilis, Eruptive—Collected by Dr. William Pepper
45. Syphilis, Softening of the Brain—Collected by Dr. I. Cain of Charleston, S. C. (3 extra pages of notes)
46. No specimen, but notes on Tinia capitis

It is difficult to contemplate any object belonging to the past without experiencing some kind of emotion, and the more unusual the object is, and the more carefully it is considered, the more positive the sentiment becomes and the more complex it seems. Serious attention to the portfolio was attracted solely through the name of the donor. When one remembers that Dr. S. Weir Mitchell was a leading citizen of Philadelphia for almost half a century, a physician of internatonal reputation, the author of many scientific and medical contributions, a poet, the writer of many novels and short stories, and that he was twice president of this College of Physicians, how can one escape the conviction that, if such a man was once the possessor of this collection of mounted hair, and if he deemed it worthy of presentation to The College of Physicians, it must be an object worthy of attention and sentiment regarding it may not be wasted?

What could have been Mitchell's interest in this hair? How did he come to present it to the College? When did he do it? There is mystery regarding that date *1851* upon the old cover of the portfolio. It could scarcely have been the date of the presentation, for at that time Mitchell was only twenty-two years old, and had been graduated in medicine only one year. He could not have been greatly interested in the College, for he was not elected to fellowship until 1856. His name does not appear among those by whom the specimens of hair were collected and presented to be mounted by Browne. But his father's name

does: the specimen of "Plica Polonica" was "Presented by Prof. J. K. Mitchell." Perhaps his interest in hair, if he had any, was, like the portfolio, inherited from his father and, thus, more sentimental than practical.

The greater number, twenty-three, of the specimens were collected by Dr. William Pepper. That cannot, of course, be the present dean of the Medical Department of the University of Pennsylvania, for he was not born until 1874, nor could it have been his distinguished father, Provost Pepper of the University, for he was not born until 1843, and would have been only eight years old in 1851. It must, therefore, have been Dr. William Pepper, *Primus*, Professor of Theory and Practice of Medicine, who was born in 1810 and would have been forty-one years old at this time, and at the high point of his eminent career as practitioner, consultant and Professor of Medicine.

It occurred to us that Prof. Pepper might have deputized young Mitchell, then perhaps a hospital resident, to secure those samples of hair that bear his name, and to turn them over to Browne for mounting and study. But that is highly improbable, inasmuch as S. Weir Mitchell seems never to have been a hospital resident, but to have gone for a year or two to Paris for advanced instruction shortly after graduation.

The bibliographies of John Kearsley Mitchell, Silas Weir Mitchell and William Pepper (*Primus*) given in the Index Catalogue of the Library of the Surgeon General present no titles suggesting interest of any kind in hair, or studies of hair.

All this leads to the conclusion that Peter A. Browne himself was the really interested person, and that, although his name usually appears as the preparateur of the specimens, they were sometimes painstakingly studied by him. Who was this Peter A. Browne?

Peter Arrell Browne, who here becomes the hero of our story, was the descendant of Quaker colonists who arrived in Philadelphia in 1683, and the youngest of the eleven children of John Browne and Mary Arrell Browne.[1] Mr. John Browne, his father,

[1] A casual mention of the portfolio and of P. A. Browne by Miss Janet Higgins, the Curator's assistant, to Miss Bishop, of the library staff, led fortunately to correspondence

was a Whig of the Revolution, and a member of the first "Committee of Safety" in 1775. He afterwards went into the army and was promoted to the command of a battalion, and distinguished himself at the battle of Germantown.

Peter A. Browne was born near Front and Vine Streets in the Northern Liberties, Philadelphia, April 20th, 1782. He was educated in Philadelphia and read law with Samson Levy, Esquire, being admitted to the Bar on March 7th, 1803.

Soon after his admission to the Bar, he was called upon to defend the unfortunate Lieutenant Richard Smith, who was charged with the murder of Captain Carson, and conducted the case with singular ability. He subsequently defended James Wood, charged with the murder of his daughter. In this case, the plea of insanity was introduced for the first time and with success. He afterward advanced it again when he acted as senior counsel in the trial of Singleton Mercer for the murder of Hutchinson Heberton. "His successes in these cases have perhaps done much to make the trials of murder cases mere judicial farces."

In 1811 he was appointed Solicitor for the District of Spring Garden, and in 1825 admitted to practice before the Supreme Court of Pennsylvania. He was also Solicitor for Philadelphia County in 1845–6. He did not confine himself to criminal law, but prepared several volumes of "Law Reports" and one on "Equity" still occasionally referred to.

In 1813, together with Colonel Clement Biddle, Browne formed a volunteer military company called the State Fencibles. In 1820 he was made Colonel of the 81st Regiment of Pennsylvania Militia.

On August 12th, 1827, Browne was given command of 300 special constables sworn in to suppress a riot between the whites and blacks near the Pennsylvania Hospital, where they destroyed the building containing the flying horses.

---

with Mr. P. A. Browne, of Philadelphia, a great-grandson of our subject. We are truly grateful to Mr. Browne, who has put us into possession of so many facts that it has been difficult to add anything important to them.

In 1831 he petitioned the city council to lay gas pipes in Carpenter Street and Lodge Alley crossing Seventh Street to light the Masonic Hall and Arcade.

In 1832, when an attempt was made by a political mob to tear down the Bolliver House on Chestnut Street adjoining the Arcade, Browne, singly and unarmed, rushed into the exasperated crowd, seized the ringleader and dragged him out, thus checking the mob and probably saving the building from destruction.

Browne was one of the founders of the Academy of Fine Arts of Philadelphia and of the Franklin Institute. He delivered the oration at the laying of the cornerstone of the building of the Franklin Institute on Seventh Street below Market Street, on June 8th, 1827, and was its first corresponding secretary. In this capacity, on June 2nd, 1825, he addressed a pamphlet to the "Citizens of Pennsylvania urging as a supplement to the primary schools then in operation, the establishment, throughout the state, of classes in Science and Mechanical Arts similar to those conducted in Philadelphia by the Franklin Institute."

He was also a trustee of Lafayette College, from its inception until 1849, and for ten years (1837–1847) its Professor of Mineralogy and Geology. In 1831 he was appointed Professor of Geology in the Cabinet of Natural Sciences of Montgomery County, and in 1832 became a member of the Geological Society of Pennsylvania. He amassed a large collection of rocks and minerals, still in the possession of members of his family.

In 1847 he published a pamphlet, *An Attempt to Discover Some of the Laws which Govern Animal Torpidity and Hibernation*, which he read before the Association of American Geologists and Naturalists, at a meeting held in Boston in September of that year.

He became a member of the Academy of Natural Sciences in 1841 and remained a member until his death. "During the first ten years of his connection with the Academy he made a number of communications upon botanical terminology, supposed human footprints, the hair of man and other mammals, etc., that were published in the Proceedings for '42, '44, '50 and '51." In 1850 he wrote "Classification of Mankind by the Hair

and Wool of their Heads," and in 1853 "Trichologia Mammalium; or a Treatise on the Organization, Properties, and Uses of Hair and Wool," etc.

Browne lived at 180 Chestnut Street. He died June 7th, 1860, at the age of seventy-eight years, and was buried in St. Peter's churchyard, Third and Pine Streets, Philadelphia.

Browne's interests, as has been shown by the foregoing, were many and highly diversified. He erected a pagoda at Fairmount, in his day a place of resort, and projected the "Arcade" to which reference has been made. He is said to have been a fine linguist, a "belles lettres" scholar, and to have had an extensive acquaintance with history and philosophy. He frequently lectured and wrote upon scientific subjects.

Browne was a botanist, a mineralogist, a geologist and a publicist as well as a lawyer, and he attained to a number of unusual honors. Some institution conferred the degree of LL.D. upon him; the "Society of the Immortals" conferred membership upon him and he was elected to membership in the Société Impériale Zoologique d'Acclimatation. He was also a Past Master of St. John's Masonic Lodge.

From what he left in the way of writings and collections it would seem that his interest in hair was earnest and long continued. After his death the collection of hair was presented by his widow to the Academy of Natural Sciences.

The present Mr. Peter Arrell Browne[2] mentions two collections of hair in addition to ours, the existence of which he did not know, one of which was presented to the Academy of Natural Sciences of Philadelphia, the other to the Smithsonian Institution at Washington.

Because of our desire to be able to compare the respective merits of our collection of "pile" with the others mentioned, letters passed between our Museum and the Smithsonian Institution, and it was learned that Mr. Browne was mistaken, for nowhere in any of the various sections of that institution could any such collection of hair be found, nor was there any evidence of its ever having been there.

[2] See footnote 1.

At the Academy of Natural Sciences, however, things were different. The Philadelphia Press, shortly after Peter Arrell Browne's death and the presentation of the collection to the Academy by Mrs. Browne, published the following:

Hair that represents the crowning glory affectioned by mankind in all parts of the world was placed on exhibit for the first time yesterday in the Academy of Natural Sciences. It is the famous collection gathered by the late Peter A. Browne and included also some very interesting samples of wool.

In the exhibit is hair taken from the heads of all the Presidents of the United States, from George Washington to James Buchanan, with the autographs of many of these men. Besides the hair of Presidents, there is in the exhibit samples of the hirsute adornments of many of the early Governors of Pennsylvania and noted men of the United States who lived prior to 1856. The latter includes Major-General Winfield Scott, Henry Clay, John C. Calhoun, Vice-President of the United States, James A. Bayard of Delaware and Charles Wilson Peale, the founder of the Philadelphia Academy of Natural Sciences.

One of the curiosities of the collection is hair from the head of Rev. Andrew Marshall, of Savannah, Georgia, who was then a former slave 100 years old.

Other interesting parts of the collection are hair from Japanese, Chinese, Malay and American Indian tribes and native tribes of the Sandwich Islands, New Zealand and Tasmania. Besides these there is the most complete specimens of wool from domestic sheep and wild goats from all over the world.

The presentation of the collection to The College of Physicians by Dr. Mitchell seems to have passed without comment, but not so that to the Academy of Natural Sciences, as we find in its Transactions for October, 1860, the following:

PROCEEDINGS OF THE ACADEMY OF NATURAL SCIENCES

October 2, 1860

Mr. Cassin offered the following resolutions, which were adopted:

Resolved, That the thanks of the Academy be presented to Mrs. Peter A. Browne, for the interesting and valuable collection of the hair of man, and of inferior animals, made by her late husband, an esteemed member of this Academy, and presented by her this evening.

Resolved, That the right of giving orders for admission, and of endorsing tickets of admission to the Museum of this Academy on public days, be hereby conferred on Mrs. Peter A. Browne, and that she and her immediate family be invited and authorized to visit the Hall and Library of this Academy whenever they think proper.

The "Browne Collection of Pile" in the Academy of Natural Sciences is preserved in three especially made tin cases measuring

about twelve by eight by six inches, in which there are about a dozen large portfolios, filled with what seem to be thousands of specimens of mounted hair from every kind of human being, and almost every kind of lower animal. Years of unceasing effort, correspondence throughout the world, indefatigable solicitation and infinite pains must have gone into its assembly and preparation! The Mütter portfolio shrank into insignificance! It now becomes easy to conjecture its story: Browne, anxious to make comparisons between hairs from normal human beings and those suffering from various diseases, no doubt secured the coöperation of his medical friends, Drs. Mitchell and Pepper, and in return for what they gave him, had given them mounted duplicate specimens, together with such notes as resulted from his studies, and had added a few rare and curious human specimens, together with some samples of his beloved wool, that he thought might interest them.

Let us now turn to Browne as he reveals himself in his work — a copy of *Trichologia Mammalium* was found in our Library. So far as is known it has never been asked for by any reader, and yet it is just the kind of book that so versatile and remarkable a man might be expected to write. The scope is broad, the style quaint though lucid. It is scientific throughout. The work is dedicated "To the Honorable, The Senate and House of Representatives of the Commonwealth of Pennsylvania," and was published "Under the Patronage of the Commonwealth of Pennsylvania."

In an essentially technical work such as this it is difficult to derive an insight into the character of a man through his method of expressing himself in print; but fortunately before the dull science begins the author opens his heart in a

PREFACE

Natural History includes *all* the works of the Mighty Creator; her votaries with the aid of the telescope, measure the parallax of the most distant stars, and, with the microscope, scrutinize the minutest portion of the smallest infusoria, plant, or crystal. Nothing for them is too large, nothing too small for examination, which God has placed within their reach. If the Deity has not deemed it beneath *His* dignity to *create* an object, surely it would be presumptive in man to consider it too insignificant for *his* study. Then let no one marvel that we have devoted so much time to ascertain the organization,

properties and uses of hair and wool. To the unreflecting, this department of knowledge may, at first view, appear to be trifling; but, with each successive advance, it will acquire more importance.

The Science which relates to Pile may be called Trichology, (from Trix, a hair;) its descriptive part is Trichography. It is a branch of Zoölogy, or rather of Mammalogy; and, so far, it is connected with Physiology, Anatomy and Comparative Anatomy. Some of its discoveries shed new light upon the ethnological problem of the unity of the human species, and others will be found to be intimately connected with those branches of agricultural industry, which relate to the raising of Sheep and producing of wool, and the raising of Swine for the bristles. It embraces a large field of inquiry, many parts of which are yet only partially explored.

In our progress we have endured considerable mental labor and encountered some unexpected difficulties; but cheered by the countenance and aided by a few scientific friends, we have pursued a steady course, and have, at length, brought our examinations to a tolerably successful termination. It will be recollected that we were obliged, in the first instance, to collect the *materials;* and, after years of untiring exertions, we have at length the largest and most valuable known cabinet of pile. In the meantime we attended lectures on Physiology and Anatomy. We have made use of none but superior instruments, and some of these are entirely new—either in themselves or their application to this study. We have availed ourselves of the researches of those who have gone over the ground before us, at all times acknowledging their truthfulness and pointing out their errors. We have carefully preserved the specimens from which our drawings are made, for future re-examination, if desirable. Upon a theme so extensive, and comparatively so novel, we do not expect to have escaped error; but we trust that when pointed out, we shall ever be found ready to acknowledge and correct them.

P. A. Browne,
Philadelphia.

Beginning with Chapter I, Part 1, we read:

Of the Word Pile.—There is no English term, in common use, which includes *hair* and *wool;* we have, therefore, adopted the word "Pile", (from "pilus", a hair). It is true that there are some animals, (belonging partly to the *Carnaria*, and partly to the *Rodentia*,) upon whose bodies are found both hair and wool, that are called "the *fur*-bearing animals", from which some might infer that "*fur*" is a generic term, including both these integuments; but there are *other* animals, upon whose bodies are found both hair and wool, that are not so denominated, wherefore it would have been improper to have placed the word "*fur*" at the head of this Chapter.

Of the Definition of Pile.—We have never seen an accurate *definition*, nor even an exact *description*, of pile, hair or wool.

A definition, to be logical, should furnish a general idea of the nature of the *genus* of the object defined, with *all* the essential *specific* differences. To do this we are not, *at present*, prepared. But a *description* may pass examination, if it contains *the most remarkable* properties of the object described. This we shall attempt to make with the word *pile*.

It is now evident where we derived the word "pile," and as it seems to have met with so cold a reception as to have almost completely disappeared, we have entitled this paper "The *Resurrection* of Pile."

It takes three and a half pages of the Table of Contents simply to list the subjects treated, almost any of which might form the starting point of an interesting presentation in itself. The modest Preface gives no inkling of the vast extent of erudition, observation, literary allusion, experimentation and cautious generalization to be displayed in the text. Nothing seems to have escaped the author. Listen to a few of the subjects picked out by the eye as the pages are turned: "The difference between hair and wool, between wool and fleece, between pile and feathers"; "The description of a feather"; "The turkey's beard"; "The pile of the Ornithorynchus, that bears the strongest resemblance to a feather"; "The mantel and hair-like processes of the armadillo"; "The pangolin or manis scales and the hair-like processes that grow between and beneath them"; "The scales of the prehensile tails of some of the lower animals and the hairs accompanying the same"; "The horn of the rhinoceros"; "The spines of the porcupine"; "The whiskers of the rabbit and of the opossum"; "Of bristles"; "A bristle of a Russian wild boar"; "The mane of the lion"; "The mane of the horse"; "Tail hairs of the hippopotamus".

"Of the different parts of pile—the button; point; cortex, squamose and paved; intermediate fibres and fibrils; center solid, canal, with granulated substance, with and without pigment cells; the follicle, its sheath, vessels, etc." Each of these parts is carefully described.

With respect to a specimen of "Wool from the Uterus of a Black Woman [studies of which were] made 10th of April, 1849," and of which there is a specimen in our collection, he says:

"Whence came this pile? Are we to presume that its germ came from one of her parents, that it was transported by the circulation and absorbed in the placenta by the radicules of the ambicular vein? Or was it a spontaneous generation? Or was it forced in from without?"[3]

He does not answer any of the questions, however!

An instrument invented for the purpose of determining the "ductility, elasticity and tenacity of pile" is very ingenious. He calls it a "Trichometer," and the accuracy with which he made his computations is indicated by the directions for its use which begin, "Having ascertained the state of the barometer, thermometer and hygrometer," etc.

The notes upon the comparative length of the hairs of the lower animals contain a list of thirty animals, of whose pile it seems worth while to mention only that from the tail of aYak; the mane of a lion; the hair on the side of a polar bear; the bristle of a Russian hog; the long hairs on the ferret, possum and stone martin; the fur of a chinchilla; the fur of a black jennet; the fur of the ermine and the fur of the mole.

Considerable space is devoted to the normal anatomy and physiology of the hair, followed by studies of pile in a variety of diseases. Here we find mention of many types represented in our collection, such as those allied with softening of the brain, presented by D. I. Cain, M.D., Charleston, S. C. and those allied with the last stages of coxalgia, presented by Dr. William Pepper. Of the specimens credited to Dr. William Pepper, all were carefully studied. At the close of this section he adds: "The above specimens of diseased hair were presented by us to the Jefferson Medical College of Philadelphia."

Can he have meant that they were presented to Dr. John K. Mitchell of the Jefferson Medical College, from whom they passed to Dr. Silas Weir Mitchell?

The pile of lunatics was studied through the assistance of "Dr. Kirkbride of the Pennsylvania Insane Hospital, who politely sent us twenty specimens of these tegumentary appendages, *cut* from the scalps of as many unfortunate beings, both male and

[3] P. A. Browne, *Trichologia Mammalium*, p. 98.

female, of various ages, and laboring under different kinds of insanity." He also made "an examination of twenty-one specimens of the hair of lunatics, presented by Dr. Evans, made in August and September, 1849." As all of these supposedly morbid hairs were "examined" and submitted to the trichometric method of observation, it might be supposed that some facts of importance would be discovered, but nothing seems to have come of it. In the book the figures referring to the "ductility, elasticity and tenacity" are given in every case, and in our portfolio some of the specimens are followed by extra sheets of notes. But in no case does it seem that the hairs of the diseased differed essentially from the normal, and in his book Browne makes no generalization regarding constant differences between normal hair and hair from the diseased, or differences between hairs in different diseases.

He *did*, however, believe that he had made a discovery with respect to the hairs of lunatics and speaks of it as follows:

> From the whole of these examinations, we feel satisfied that if there exists *any difference* between the hairs of the sane and the insane, it must be sought for in the *button*. It will be recollected, that this portion of a perfect hair of the head of a sane white person is translucent, and of a regular shape—generally that of a pestle.
>
> When a hair is *drawn* out of the head, we sometimes have the *stalk* only—the button, sheath and follicle, being all left behind. This is more generally the case when the dermis or epidermis, owing to disease or any other cause, is contracted; and this, probably, will account for the large proportion of hairs of the insane, which came under examination, being *without a button*. Upon three hundred and sixty-nine hairs, presented by Dr. Evans, we found but seventy-nine buttons—and this occurred after a careful drawing; and upon one hundred and fifty-eight hairs obtained from Dr. Kirkbride, there were fifty buttons. Upon an equal number of hairs, carefully drawn from the head of a sane, healthy white person, probably there would have been three-fourths with a button.
>
> It will be perceived that out of the 139 buttons examined by us, thirty-eight had the ordinary, and 101 distorted and discolored buttons. The distortions have *no general character*, some of them are flattened, others are crooked, curved or twisted and there are a few that are hamate [hooked]. There is a loss of the translucency, which is characteristic of the button of a sound hair. (Since writing the foregoing, we have examined a great many hairs of lunatics from the Asylum in Staunton, Western Virginia, and from two lunatic asylums in

Ohio, and found the results always the same.)[4] We do not, nevertheless, pretend to have extended our examinations to the length that would authorize the enunciation of a theory; but, on the contrary, make the result of our labors known, merely to attract the attention of medical gentlemen, and particularly those who are connected with insane asylums, to the subject. Should future inquiries confirm our views, it will appear that in lunacy the *skin* and its *appendages* are affected, and these distortions and discolorations of the button may become valuable diagnostics. It has been shown that the button and the follicle, as well as the shaft of the hair are continually forming from cells, to supply the deficiency caused by the gradual waste from hairs falling out; and this explains why *a part* only of the hairs examined were distorted and discolored, while the remainder were in the ordinary state.

The hairs of *lunatics* were the first diseased ones which came under our examination, and it is possible that we may have mistaken for the signs of *lunacy* what were the marks of *disease only*. If this shall turn out to be the case, the error can easily be corrected by comparison with other diseased hairs.

We are assured by Prof. Dunglison (in Hum. Philos., p. 227,) that, "Mania never occurs without the physical condition of the brain undergoing some change, directly or indirectly," and that, also, "the *cranium* is often affected, seeming, for example, to be unusually thick, dense and heavy." Then, what is there incredible in the idea that it affects the *skin* and *hair of the head?*

All that we have to say, in conclusion is—do not decide upon the merit of our discovery until you have examined the subject.

"Finis coronat opus".[5]

"The Decay and Death of Pile" discusses baldness; "Of the growth of the Hair after death" several examples are given.

Chapter VII opens with the statement: "Hair that has been separated from the body of the Animal never acquires a distinct life. It has been supposed that a hair, laid for some time in a stream or pool of water, is transformed into a *worm*; but this is a popular error. It will *appear* to be animated; but that is owing to animalcules with which it becomes invested. There is an annelida called 'the *hair-worm*' (Gordius Aquaticus,) which is found in stagnant pools, and this *name* has probably aided in propagating this error."

Interesting remarks are made about the "Electricity of Pile"; "Pile as a conductor of Caloric"; the "Effect of climate and seasons upon Pile"; "Incineration of Pile"; "Fossilized Pile";

[4] In the original this sentence is a footnote to the preceding sentence.

[5] Browne, *op. cit.*, p. 122.

the "Hygroscopic Property of Pile". Here he makes a most entertaining reference to historic and romantic literature thus: "When Capt. Bligh made his perilous voyage, in an open boat, over three thousand miles of the ocean, he and his companions used to dip their clothes in the sea and wear them damp, to allay the desire for drink. It is generally supposed that the moisture was absorbed through the *pores of the skin.* We would rather ascribe the quenching of the thirst to the *inhalation* of the aqueous vapor, caused by the heat of the body, but think it *possible* that a very small portion may be absorbed by the hair."

Sixteen years after the publication of Browne's book, Emile Richard Pfaff, who wrote "Das menschliche Haar" (1869), yielded to the temptation, avoided by Browne, of supposing that inasmuch as the hair was of a somewhat tubular structure, it must function as such and assist the aeration of the blood through the absorption of oxygen from the air, as well as act as an organ of elimination by which volatile substances are withdrawn from the blood and passed out through the hair. Pfaff even went so far as to suppose that the miasms of various diseases might be admitted to the system through the hair, and, amusingly enough, observed that those whose vocation kept them in an atmosphere charged with the fumes from various drugs—as apothecaries—were often exempt from the danger of infection!

The anthropological importance of hair in the determination of race so profoundly impressed Browne that he devotes a considerable number of pages to it. His earlier special publications upon it are thought by many to be his most important contribution to science. He says of the classification of man by the pile of the head: "Having shown that there are three distinct species of pile of the head [A. Cylindrical; B. Oval; C. Eccentrically Elliptical], if we can prove that there are three portions of men who now exist, and who from time immemorial have existed, the covering of whose heads, respectively, do, and have, uniformly, corresponded with these three species of pile, there will be no difficulty in pronouncing that (judging from the pile of their heads) they belong to three distinct species of men."[6] This

[6] Browne, *op. cit.*, p. 59.

thesis he proved through the collection and examination of hairs from men of all races. He also describes and discusses the effects, upon the hair, of hybridizing these races.

C. H. Danforth, in one of the latest and best books upon the subject of hair, "Hair, with Special Reference to Hypertrichosis" (1925), gives full credit to Browne for this anthropological discovery and points out that *he never received the credit he deserved.* That may have been because the publication of Browne's book under the "Patronage of the Commonwealth of Pennsylvania," resulted in a limited issue with no active publisher to advertise and market it. In consequence, the credit is always given to Pruner-Bey, who, in Paris, in 1863, ten years after the publication of Browne's book, wrote "De la chevelure comme caractéristique des races humaines d'après des recherches microscopiques." This work immediately reached the whole scientific world, and everywhere Pruner-Bey is quoted and Browne eclipsed! Fortunately Browne died in 1860 and did not live to find himself robbed of the credit he so justly deserved and which it is our pleasure to accord him.

College Notes

Elections to Fellowship (October 4, 1939):

George W. Chamberlin, Emmet Frederick Ciccone, Van Mashburn Ellis, Philip J. Hodes, Malcolm W. Miller, Ella Roberts.

Necrology:

Herman B. Allyn. November 6, 1939.
David R. Bowen. September 6, 1939.
Albert C. Buckley. August 17, 1939.
Charles N. Davis. October 20, 1939.
Louis D. Englerth. August 16, 1939.
Collin Foulkrod. November 16, 1939.
Charles P. Grayson. August 16, 1939.
William J. Mayo (*Honorary Fellow*). July 29, 1939.
J. Milton Miller. July 6, 1939.
Thomas R. Neilson. October 25, 1939.
James J. Quiney (Non-resident Fellow). March 31, 1937.

Act of the Council on a Public Matter:

On November 29, 1939, the following communication, signed by the president and the secretary of the college, was sent to the Hon. Robert E. Lamberton, mayor-elect of the city of Philadelphia:

"The College of Physicians of Philadelphia by action of its Council at a meeting held November 28, 1939, urges upon the Mayor-Elect of the City of Philadelphia the selection for the position of Director of Public Health in the City of Philadelphia of a qualified public health officer who shall be a doctor of medicine qualified both by special training and by experience in the field of public health."

Hatfield Lecture (May, 1940):

The Nathan Lewis Hatfield Lecture on May 1, 1940, will be delivered by Robert B. Osgood, M.D., John B. and Buckminster Brown professor of orthopaedic surgery, emeritus, Harvard Medical School, the title of the lecture being "The Medical and Social Approaches to the Problem of Chronic Rheumatism."

Recent Publications by Fellows:

(The names of Fellows are marked by an asterisk.)

Bergey's manual of determinative bacteriology. By David H. Bergey*†... A. Parker Hitchens,* *et al.* 5 ed. Baltimore, Williams & Wilkins, 1939.

*Cantarow, Abraham, and Max Trumper. Clinical biochemistry. 2. ed. Phila., Saunders, 1939.

*Chance, Burton. Ophthalmology. New York, Hoeber, 1939. (Clio medica . . . v. 20.)

† Deceased.

Jackson, Chevalier, and Chevalier L. Jackson. Cancer of the larynx. Phila., Saunders, 1939.

Martius, Heinrich. Gynecologic operations and their topographic-anatomic fundamentals. Authorized English translation under the editorial supervision of W. A. Newman Dorland* (N.-r. F.). Chicago, Debour, 1939.

Mitchell, A. Graeme,(N.-r. F.), *et al.* Pediatrics and pediatric nursing. Phila., Saunders, 1939.

Mock, Harry E., *Pemberton, Ralph, and John S. Coulter. Principles and practice of physical therapy. 3 vols. Hagerstown, Prior, 1939.

*Murphy, Douglas P. Congenital malformations. Phila., priv. printed, 1939.

Prinz, Hermann, and Sigmund S. Greenbaum.* Diseases of the mouth and their treatment. 2. ed. Phila., Lea & Febiger, 1939.

*Reimann, Hobart A., *ed.* Treatment in general medicine. 3 vols. & index. Phila., Davis, 1939.

Robertson, Wm. Egbert, and Harold F. Robertson, *eds.* Diagnostic signs, reflexes and syndromes. Phila., Davis, 1939.

*Spaeth, Edmund B. Principles and practice of ophthalmic surgery. Phila., Lea & Febiger, 1939.

The Library

Beginning January 7, 1940, and continuing through April, the library will be open on Sunday afternoons from 2 until 5:30 o'clock. This marks the first time in the history of the College, so far as we know, that the library has been open on Sunday; the Library Committee and the Council of the College trust that the Fellows will welcome these additional hours, during which, it is assumed, many have greater opportunity for reading and study.

Through the generosity of Dr. Charles W. Burr, the library has recently acquired a microfilm reader. The Bibliofilm Service, in Washington, is prepared to supply, at very reasonable cost, a microfilm copy of any work in the Army Medical Library, the Library of Congress, and other great libraries, for reading on this machine. The need for borrowing volumes on inter-library loan is, therefore, greatly reduced, to the advantage of the lending library, and readers are able to consult material which would not be sent on loan in its original form under any conditions. All arrangements for obtaining microfilm copies of material not in the College library may be made at the circulation desk in the Reading Room.

RECENT ACQUISITIONS OF SPECIAL INTEREST

Incunabula

Salicetus, Nicolaus. Antidotarius animae. Strassburg, Grüninger, 1494. (Hain 14164?) Gift of E. B. Krumbhaar, M.D.

Valle, Robertus de. Compendium memorandorum Plinii. Paris, Baligault, 1500. Pell-Pol 4537. Klebs 357.1. Gift of Charles W. Burr, M.D.

Other Books

Cervetto, G. Di alcuni illustri anatomici Italiani del decimoquinto secolo. Verona, 1842. Gift of Burton Chance, M.D.

Luisinus, Aloysius. De confessione aegrotantium. Venice, 1563. Gift of Burton Chance, M.D.

del Valle y Aldabalde, Rafael. La mujer: representación gráfica de su estructura . . . con un texto explicativo. Madrid, (n.d.). (A modern version of the anatomical fugitive sheet.) Gift of O. H. Perry Pepper, M.D.

Miscellaneous

A portfolio of portrait-etchings of Philadelphia physicians; a portfolio of anatomical drawings; both, the work of the late Erwin F. Faber. The portraits and drawings were mounted, and the portfolios supplied, by Samuel Booth Sturgis, M.D. Gift of Mrs. Erwin F. Faber, through Balduin Lucké, M.D.

A contemporary print of the Civil War "Satterlie" Hospital in West Philadelphia. Gift of Sigmund S. Greenbaum, M.D.

A group of early 19th century physicians' bills and other medical documents, including a printed schedule of fees adopted by this College in 1824. Gift of O. O. G. Lewis, D.D.S., through Robert H. Ivy, M.D.

A lecture-admission card signed by George B. Wood, M.D. Gift of Horatio C. Wood, M.D.

Photographs of a sketch and an oil painting of Benjamin Say, M.D.; photographs of a sketch of the figure of Benjamin Rush, M.D., in the painting by E. A. Abbey in the House of Representatives, Harrisburg, Pa. Gifts of William N. Bradley, M.D.

The Committee on College Collections

RECENT ACQUISITIONS

Twenty-one etched steel or copper plates, the work of the late Erwin F. Faber. Gift of Mrs. Erwin F. Faber, through Balduin Lucké, M.D.

Early, unsigned, minature oil portrait (after the painting by Sully) and silhouette of Benjamin Rush, M.D. Gift of George P. Muller, M.D.

Etched copper plate, by the late Erwin F. Faber, of George W. Norris, M.D. Gift of William N. Bradley, M.D.

Framed colored drawing, by Lazar Raditz, of George W. Norris, M.D. Gift of Mrs. William Fisher Norris.

Bronze medal of Theobald Smith, made for the third International Congress for Microbiology, 1939. Gift of Herbert Fox, M.D. Another copy, the gift of Balduin Lucké, M.D.

Bronze medal of Robert Walter Doyne, F.R.C.S., made for the Oxford Ophthalmological Congress, 1917; the favorite cane of George M. Gould, M.D. Gifts, by legacy, of Laura Stedman Gould Dees.

Certain Ovarian Tumors Associated with Sexual Endocrine Dysfunction*

By Howard T. Karsner, M.D.

Professor of Pathology, Director of the Institute of Pathology, Western Reserve University and University Hospitals, Cleveland, Ohio

INTRODUCTION

Tumors of the ovary have manifestations in common, which depend upon situation and size, effects upon circulation and upon nerves, pressure upon ureters and intestines, rupture of cystic cavities and torsion. There are, however, certain ovarian neoplasms which may exhibit, in addition, special endocrine phenomena. The ensuing discussion of these special tumors requires a review of the embryology of the ovary, the clinical and pathological effects, the histogenesis of the lesions, and their particular endocrine disturbances.

EMBRYOLOGY

There are certain differences of opinion as to details of the development of the ovary. It is agreed that in the genital ridge there is a condensation of epithelium of the celomic cavity and that under this there is in the mesenchyme an early differentiation of a dense cortical zone, a clearer medullary zone and, near the hilum, the precursor of the *rete ovarii*. It has been held that the celomic epithelium, the so-called germinal epithelium, produces ova, granulosa and other elements of the mature ovary. Fischel's study, conducted with modern methods and meticulous care, indicates that the surface epithelium does not produce Pflüger-Valentin tubules, nor does it contribute in any way to the substance of the ovary; it merely persists as a covering layer. According to Fischel, the primitive sex-cells arise in the entoderm of the hind gut, wander into the surface epithelium of the ovary

* Thomas Dent Mütter Lecture LII, The College of Physicians of Philadelphia, December 6, 1939.

and thence into the early sex gland. There they multiply to produce ova. Sex-cords and medullary cords differentiate from the mesenchyme of the sex gland anlage. The same is true of the cells which surround the primordial ova, which later become the granulosa of the developed graafian follicle. It is probable, however, that the presence of primitive sex-cells in the surface epithelium influences the differentiation of the mesenchyme and that the ova in some way determine the differentiation of the granulosa. Indeed it is claimed that granulosa is wholly dependent, for its normal growth, upon the presence of the ovum. In the gonad destined to be ovary, the germ cells are widely diffused. The sex-cords break up into fairly uniformly distributed ball-like masses, enclosing ova. These masses appear under the surface but are not connected with it. The intervening tissue forms the ovarian stroma and the ball-like masses are subsequently arranged to form the so-called primordial follicles, which only later become true follicles of cyst-like character. The *rete ovarii* is a remnant of a process of condensation of mesenchyme which produces first cords and later, in some instances, tubules. The cords and tubules are blind but originate in the hilum of the primitive ovary and extend laterally to interlace, but not to communicate, with the primitive renal tubules. Ova may be found in these cords, but soon disappear.

Of probable significance is the fact that the ovary develops in the same region as do the kidney, adrenal gland and segments of the spinal column. In connection with neoplastic growth in general, a knowledge of the embryonal development of the tissue involved is essential to any understanding of the genesis of tumors. This is emphatically true of the ovary, the varied tumors of which present most complex problems of oncogenesis.

The Special Tumors

Granulosa-cell tumor
Luteinized (luteoma)
Theca-cell tumor
Arrhenoblastoma
Adrenal tumor (hypernephroid)

Dysgerminoma
Brenner tumor

The tumors associated with disturbance of sex hormones are spoken of as feminizing and masculinizing, but tumors of essentially the same morphology may have no such effects. The typical feminizing tumor is the granulosa-cell tumor. Similar effects may accompany the luteinized granulosa-cell tumor (luteoma) and the theca-cell tumor. The masculinizing tumors are the arrhenoblastoma and to a certain degree the so-called hypernephroid tumor. Another tumor, apparently related embryogenetically, is the dysgerminoma, but it is devoid of hormonal influences, as is true also of the Brenner tumor.

The terms feminizing and masculinizing are subject to various interpretations. Feminization is used in reference to precocious female sexual development, both morphological and, insofar as menstruation is concerned, functional. It is not certain that this is always ovulatory menstruation. The term also covers menorrhagia and metrorrhagia in sexual maturity, as well as bleeding after the menopause, but again this is not necessarily related to ovulation. According to Corner, anovulatory menstruation may occur in the human as well as in primates and uterine bleeding can be due to alterations in amount, proportion, or kind of ovarian hormones, either deprivation or imbalance of them. Thus, the bleeding is not an increase in femaleness. Feminization, as used in connection with ovarian tumors, means really precocity or increased manifestations of the phenomena of femaleness rather than an increase of femaleness *per se*.

The distinction between so-called defeminization and masculinization is difficult to draw. The former means depression of function and form as related to femaleness. The most common manifestation is amenorrhea. Atrophy of breasts is probably to be included also. In general, and in the individual case, it is impossible to say whether hirsutism is due to depression of femaleness or preponderance of maleness. Male conformation of the body and angulation of the face may well be due simply to alterations in distribution of fat. Enlargement of larynx and of clitoris are evidently true signs of masculinization.

The *granulosa-cell tumor* may be accompanied by no disturbance of sexual functions or by one of several changes. Arising in prepuberal life, it is likely to cause pronounced sexual precocity. It

is the most firmly established of the suggested causes of *pubertas praecox* in the female. In sexually mature life, it may cause menorrhagia or metrorrhagia. There may also be reduction of

FIG. 1

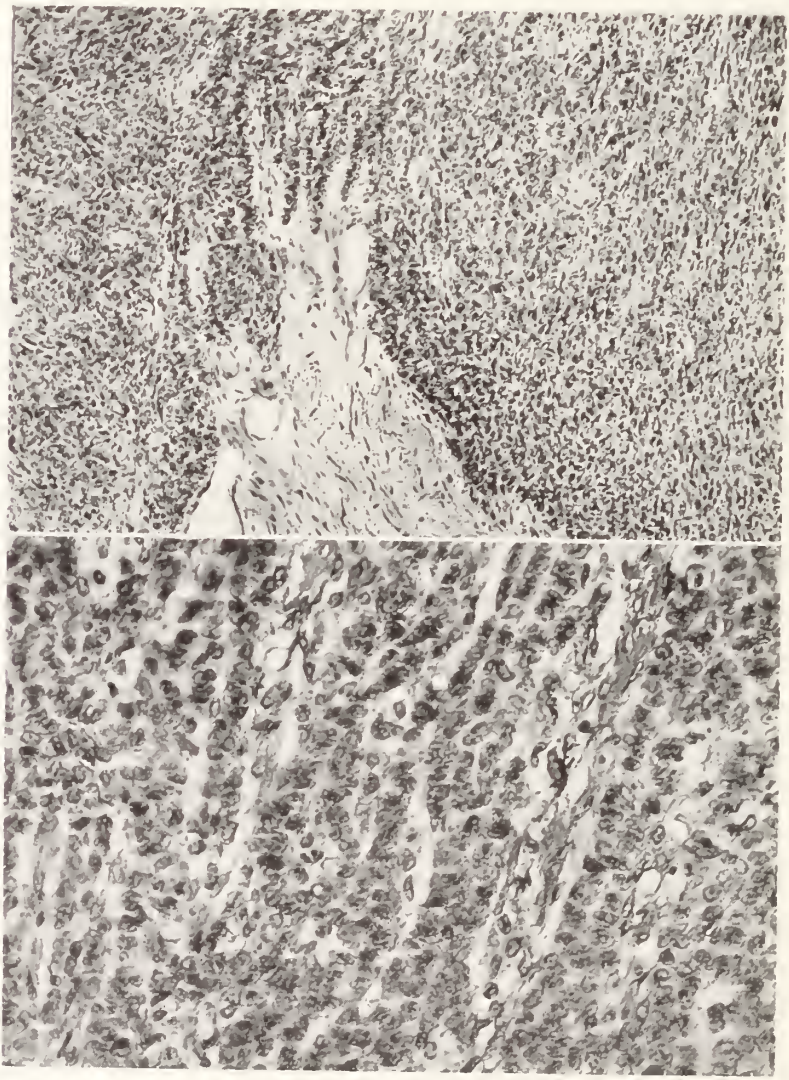


FIG. 2

FIG. 1. Granulosa-cell tumor. Low power to show diffuse type of growth and relation to loose stroma.

FIG. 2. Granulosa-cell tumor. Diffuse growth with slight trabecular arrangement.

menstrual flow and amenorrhea, the latter being accompanied rarely by hirsutism, male type of escutcheon and beard. Sevringhaus states that "in its ovarian aspects, menstrual rhythm may be disturbed by alteration in the duration or the intensity of follicular or luteal secretory activity." In the post-climacteric, beginning even many years after the menopause, this tumor tends to produce prolonged bleeding or an irregular bleeding which sometimes has a more or less cyclic rhythm. The failure to produce any sexual manifestations has been explained by immaturity of the special cells of the tumor or by their extensive degeneration and necrosis. Menstrual disturbances and metrorrhagia are not necessarily due to hormonal dysfunction; in some instances they may be due to the size and situation of the tumor.

In 48,000 surgical specimens in the Institute of Pathology, there were 492 ovarian tumors, of which 18, including one theca-cell tumor, were granulosa-cell tumors, an incidence of 3.6 per cent of the various tumorous lesions of the ovary. Novak states that they constitute 10 per cent of ovarian carcinomas. Dockerty and MacCarty found 30 granulosa-cell tumors in a total of 400 solid ovarian tumors. Bland and Goldstein collected reports of 311 cases and found the highest incidence (13.2 per cent) in the sixth decade but many also occurred subsequent to that period and also in the fifth and fourth decades. Thus, the tumor occurs most often about the time of menopause and thereafter. Klaften, in an analysis of 80 cases, found 8.7 per cent before puberty. Occurrence in early childhood is illustrated by the cases of Hunt and Simon (17 months old), Noordenbos (2 years old) and Holland and McHugh ($2\frac{1}{2}$ years old). Gross has observed one in a child 13 months old, which showed its first manifestation at 5 months of age. C. B. Lull (personal communication) will report one in a child of 9 months, who had had periodic bleeding since shortly after birth. Like other ovarian tumors, granulosa-cell tumors affect the left ovary more often than the right. About 10 per cent are bilateral. Most of the tumors are actually benign even although the microscopic picture may be interpreted as indicative of malignancy. The benign tumors may be only a few millimeters in diameter, but both benign and malignant forms

may reach enormous size, to the point of nearly filling the abdomen. "Giant size" benign forms have been removed, in spite of great operative difficulties, with complete cure (Schiller; Te Linde; Dockerty and MacCarty).

Grossly the tumor is usually nodular, but except in outspoken instances of malignancy the capsule is smooth and unbroken. The smaller tumors are solid, but the tendency of granulosa to form spaces may be exhibited by the tumor, and dilatation of these spaces leads to cyst formation. Necrosis may also produce cyst-like cavities, into which hemorrhage often occurs because of the destruction of blood vessels. Otherwise the tumors are firm, pale gray or yellowish gray in color and with a cellular appearance in the cross section.

Microscopically, it is possible to distinguish four forms; a diffuse form, a trabecular form, and folliculoid forms with or without the production of spaces suggestive of follicles. These may all occur in the same tumor. The diffuse form shows sheets and masses of granulosa-like cells, sometimes in short spindle forms resembling the cells of fibroma. The trabecular form is especially interesting because the arrangement of the trabeculae suggests infiltration and invasion, even although it is only a lack of distinction between elements of the tumor itself. The trabeculae are cords, bands and nests of cells closely resembling granulosa. Without sharp delimitation, they grade over into cells like those of mesenchyme, spindle cells of mature connective tissue type and loosely arranged stellate cells, all probably constituents of the tumor. This lack of distinction is unlike the more or less sharp line separating invading epithelial tumor from the surrounding stroma. This is the form often called cylindroid, but to the general pathologist this term as applied to tumors has a special connotation not fulfilled by the trabecular types of granulosa-cell tumor. In the folliculoid form, the masses of cells of the tumor bear somewhat the same relation to the stroma as does the granulosa to the theca. Some show only these solid masses, but others show small or large rounded spaces, filled with fluid, into which the lining cells may project in an irregular fashion, quite different from the regularity of outline of the acinar

spaces of adenoma or adenocarcinoma. Of interest are the Call-Exner bodies; tiny spaces about the size of a large mononuclear cell, empty or with a minute nucleus-like granule in the center, vaguely suggesting the appearance of an ovum. These are not confined to granulosa-cell tumors or even ovarian tumors, since they may appear in tumors elsewhere in the body. It is generally agreed that ova do not occur in granulosa-cell tumors and that the Call-Exner bodies probably represent hydropic degeneration of a cell or small group of cells.

There are two criteria of malignancy that can be applied to granulosa-cell tumors; invasion of neighboring tissues and metastasis to regions in which there is no likelihood of the independent occurrence of a similar tumor. Any recurrence must be investigated to exclude a new independent tumor. The unknown stimulus to neoplasia, which operates upon a group of cells in one ovary, may act similarly at a later time upon the other ovary. Furthermore it is conceivable that original cells of the same nature may be present in neighboring structures as the result of embryonal misplacement. W. W. Voigt reports an enormous granulosa-cell tumor of the "mesosigmoideum," the ovaries, upon palpation, being uninvolved at the time of operation.

The gross examination of the malignant granulosa-cell tumor can indicate only that it is a malignant tumor because its identification as granulosa-cell is established solely by microscopic examination. The malignant granulosa-cell tumor is usually large, and, like other malignant tumors of the ovary, likely to be bilateral. The tumor grows into and through the ovarian capsule; thus adhesion to adjacent structures occurs. The consistence is variable and the cross section often shows nodular masses associated with widespread necrosis and hemorrhage. Metastasis is principally to the peritoneum, but may be widespread, and has been reported in vertebrae (Soltmann).

There are several difficulties in the microscopic diagnosis of malignant granulosa-cell tumors. With ordinary fixation it may be difficult to distinguish between true epithelium, such as occurs in carcinoma, and granulosa cells, although Schiller points out

that the latter constitute a syncytium-like mass with poorly defined cell boundaries as compared with the definite cell boundaries usually seen in true epithelium. The trabeculae of the

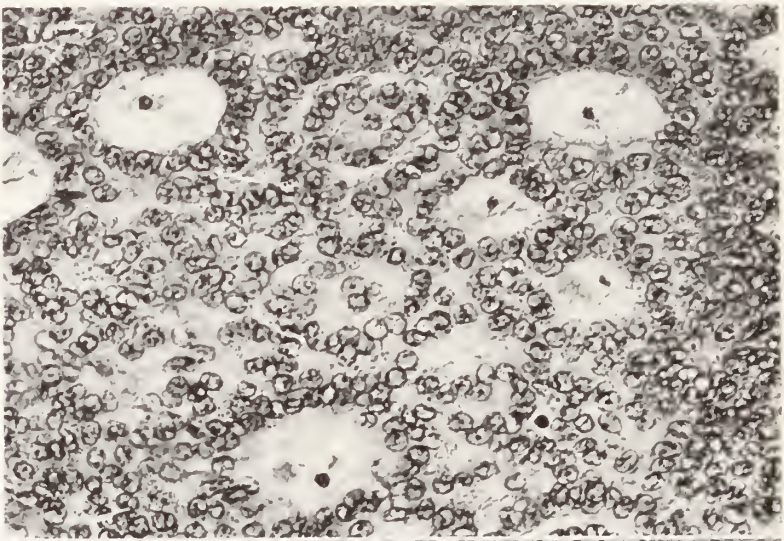


Fig. 3

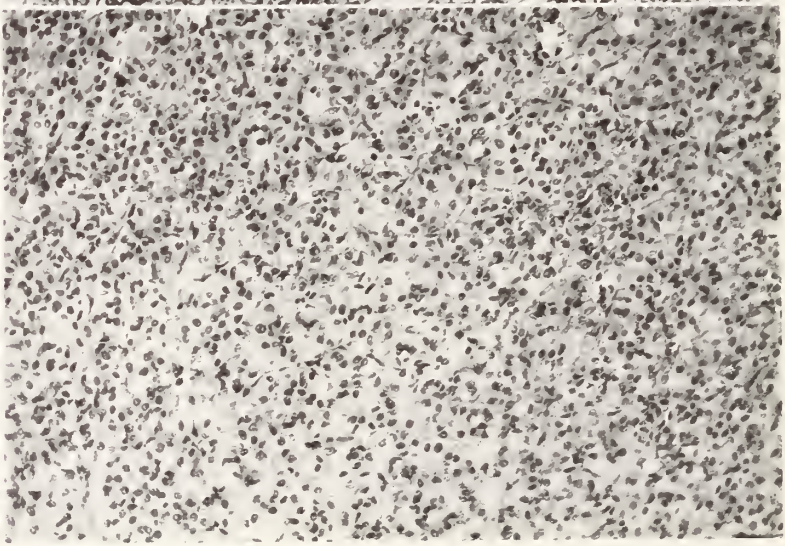


Fig. 4

Fig. 3. Granulosa-cell tumor. Formation of small spaces in folliculoid form.
Fig. 4. Granulosa-cell tumor. Luteinization in a portion of the neoplasm.

granulosa-cell tumor suggest an invasive growth, but they show a gradual merging with the enveloping connective tissue, in contrast to the customary sharp distinction of invading carcinoma. The matter of diagnosis of malignancy in a tumor clearly of granulosal type is thus confused by the frequent lack of distinction between granulosa cells and epithelial cells. A general arrangement and cellular character suggestive of granulosa cells in a tumor clearly malignant indicates malignant granulosa-cell tumor, but as Schiller states, negative evidence is also of value. This means the absence of epithelial differentiation, including cilia formation, or production of mucin, or even keratinization. Unfortunately, even this is not conclusive, for Gardner has seen goblet cells in atretic follicles and papillary growths in continuity with granulosa cells. That the goblet cells contained mucin or pseudomucin was not established. King had previously claimed that the epithelial cells of endometriosis can be derived from the graafian follicles. These observations, although not showing transformation to neoplasm, indicate the possibilities of epithelial transformation of granulosa cells. The facts available indicate that although a diagnosis of malignant granulosa-cell tumor can be made microscopically, it is rarely more than a presumptive or probable diagnosis, if made on that basis alone.

Compton's analysis of 187 cases in the literature indicates that 17.4 per cent were malignant, at least as indicated by invasion so extensive that the tumors could not be removed, by metastasis or by recurrence. In the case he reports, a recurrence was observed 16 years after the original extirpation. Schulze quotes a report by Arnold, Koerner and Mathias of recurrence 20 years after the original operation. Hückel reports recurrence after 14 years of a tumor which Kermauner and Schiller had considered to be benign. As the lesion becomes better known, instances of recurrence become more frequent and at least in part on this basis, 28, 33 and 38 per cent of the granulosa-cell tumors have been reported to be malignant. So-called recurrence is, at least academically, not necessarily an indication of malignancy. If it be assumed that there are cells in the ovary inherently pre-

pared for neoplastic change, it may well be true that the realization factor may be effective at one time in one region and at a later time in another region. Furthermore, as in W. W. Voigt's case, noted above, the tumor may arise in some situation other than ovary. Thus what may be thought of as a recurrence in the pelvis might really be a new tumor. In line with this assumption, invasion and metastasis are the true criteria of malignancy. Anything called recurrence must be of such a nature as to exclude the likelihood of a new tumor.

The tumor is often called carcinoma. The most gloomy statistics admit of cure in 62 per cent of the cases, unlike the data of other internal carcinomas. To be sure, granulosa-cell tumors have been diagnosed as benign, which really were, or became, malignant. Nevertheless there are many which are benign. The fact that they may be transformed into malignant neoplasms does not mean that they were so in the beginning. It is not good practice to call a tumor malignant because of its potentialities and no more justifiable to name all granulosa-cell tumors carcinoma than to do the same with the mammary adenoma, the papilloma of the bladder and other similar lesions.

Granulosa-cell tumors and their sub-groups are frequently accompanied by hyperplasia of the endometrium. Usually this is of cystic-glandular type, may be massive and even polypoid. Forms that do not differ from those observed physiologically also occur and may be referred to in Neumann's term as "functional," or as we designate it, "physiologic" hyperplasia. Schulze states that uterine decidual reaction has been found in 3 cases. This, however, may be erroneous because it is often difficult to distinguish between decidual reaction and other morphological changes.

Granulosa-cell tumors may be accompanied in the same ovary by fibroma, adeno-fibroma, cystoma, adenocarcinoma and teratoid tumors including dermoid cysts. Uterine fibromyomas are also common, but until this is shown to be more frequent in patients with granulosa-cell tumors than others, it seems futile to emphasize the possibility that the myomas are induced by hormonal influences upon the myometrium. The same is true

of adenomyomatosis of the uterus, even although Rockstroh in a study of 327 cases of adenomyomatosis found 2 cases with associated granulosa-cell tumor. The hyperplasia of the endometrium may suggest tumor formation but there is no indication that it ever represents true neoplasia.

Schiller discusses at length certain occasional so-called granulosa-cell tumors which contain cartilage, as well as connective tissue mucoid. Because the matrix of some of the cartilage stains as does mucoid, because of irregular arrangement of cells and lacunae, and because often there is no perichondrium, it is assumed that these areas are part of the neoplasm rather than fetal inclusions. The nature of mucoid and cartilage suggests that they are derivatives of the multipotential residual mesenchymal cells which also gave origin to the granulosa cells. The fact that such tumors may contain tubular structures somewhat like the tubules of mesonephros, suggests that the original mesenchymal cells represent a period of development prior to differentiation of the gonad and that the cartilage is from cells which might have produced intervertebral discs. The neoplasm may really be a teratoma. It is classified as granulosa-cell tumor because of its morphology; hormonal effects do not occur. Schiller suggests the name desmoblastoma ovarii, which might well take it out of the category of granulosa-cell tumor.

Luteinized granulosa-cell tumors. It is common to find in granulosa-cell tumors a certain number of cells which give the microscopic characters of luteinization. In some instances the luteinized cells are so frequent as to constitute practically the entire tumor, which has given rise to the name luteoma. There is, however, no justification as yet for placing it in a separate category, for too few instances have been reported to permit generalizations as to age distribution, functional effects, etc. Delarue and Isidor reported the presence of phospholipids but no anisotropic droplets. Traut, Kuder and Cadden, upon chemical examination, found a fairly rich content of cholesterol and its esters and a relatively small amount of phospholipid. They found only nine cases reported in the literature, and included the much discussed case of Cosacesco and his associates.

The *theca-cell tumor*, theca-lutein-cell tumor, or thecoma, has peculiarities that require special consideration. Geist, and also Melnick and Kanter, regard it as an entity. Traut, Kuder and Cadden, however, seem doubtful as to its separate identity. Collins, Varino and Weed have collected reports of 26 cases, including two of their own. Only 3 of their series occurred in women in sexual life, including their own at 22 and 24 years and one of Loeffler and Priesel's at 18 years. They do not include Brosig's two cases at 18 and 36 years nor Hammar's case at 20 years. If the case reported by Cosacesco and his associates be included, as many think it should, there would be 30 cases, of which only 6 occurred before the menopause. It is thus a disease of postsexual life and Patterson reports an instance in a patient 92 years old. In early life there is disturbance of menstruation, especially amenorrhea. In later life there is metrorrhagia, sometimes cyclic, associated with endometrial hyperplasia and even, as in Huber's case, hirsutism and cutaneous pigmentation. Cosacesco reported more definite signs of masculinization. Almost invariably unilateral and of low order of malignancy, the tumors are firm, well defined, of modest size, and resemble fibroma except for their yellow color. Microscopically, they are well vascularized and show spindle cells in sheets and bundles, which differ from ordinary connective tissue because of lipid content, as demonstrated by special stains. Geist states that these cells contain cholesterol and cholesterol esters, whereas according to Melnick and Kanter the fatty material in the granulosa-cell tumors is of the nature of phospholipid. Greenblatt, Greenhill and Brown made an examination of the lipid content of various ovarian tumors, but in most of these the amount of material available is too small to permit of exact determinations. They conclude that incretory tumors have a greater content of phospholipid and cholesterol than the nonincretory, but distinctions in the incretory group are by no means definite. My associate, Dr. R. F. Hanzal, has made chemical examination of the lipids of a granulosa-cell tumor and a thecoma, extracted in reflux condenser with alcohol. The total fat is slightly higher in the granulosa-cell tumor. The cholesterol, including free cholesterol

and cholesterol esters, is 0.757 per cent of the dry weight in the granulosa-cell tumor and 0.624 per cent in the thecoma. The phospholipids are 1.654 and 1.427 per cent respectively. These

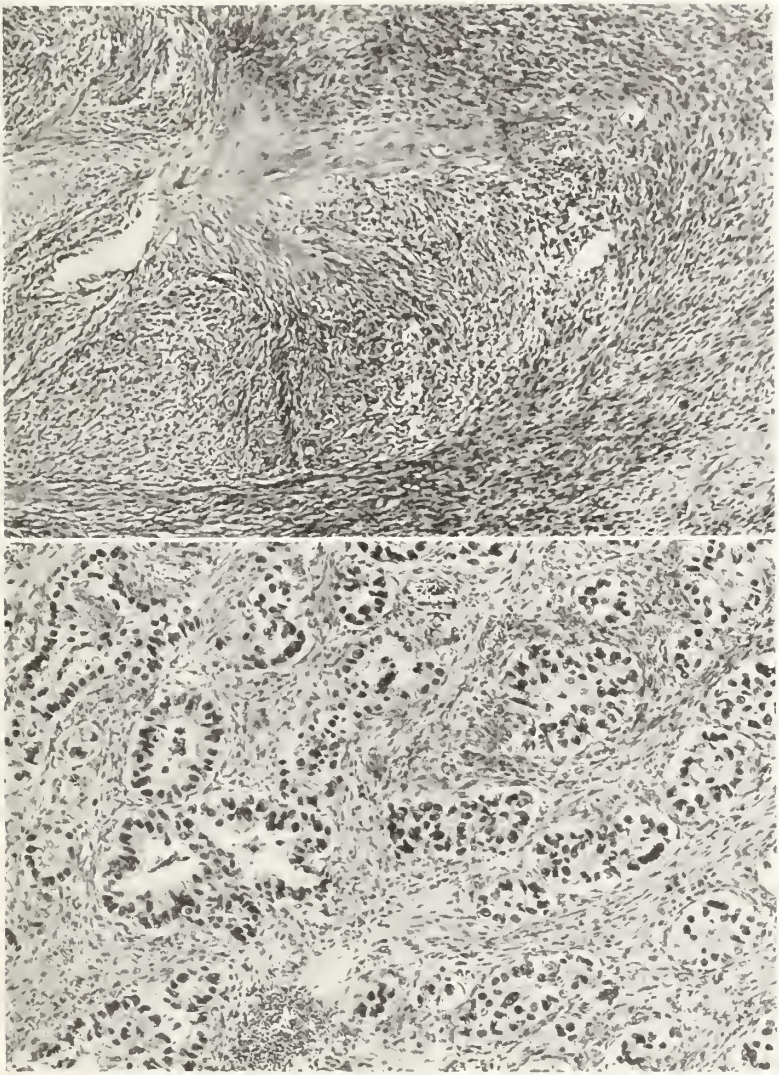


Fig. 5

Fig. 6

Fig. 5. Theca-cell tumor. Fibroma-like arrangement of cells and "hyaline plaque".

Fig. 6. Arrhenoblastoma. In this region the growth is like that of the testicular tubular adenoma.

differences cannot be regarded as significant even although 37 and 49 grams of tissue were used. The same may be said of the analyses furnished by Traut, Kuder and Cadden. Their interpretations on the basis of the Hoerr-Romeis stains go far beyond what is justified by Hoerr's publications.

The cells, as pointed out by Brosig, are individually surrounded by reticulum as is true of normal theca interna. This has been emphasized by Geist, Gaines and Pollack, by Traut, Kuder and Cadden and by Traut and Marchetti. The production of collagenous fibrils by the cells is likely to suggest fibroma or fibrosarcoma, and some have accepted the term proposed by Loeffler and Priesel, "*fibroma thecacellulare xanthomatodes ovarii.*" The fatty content, the character of the cells and the arrangement of reticulum do not positively identify the cells as thecal, but these and the morphological features strongly indicate it. Novak and Brawner, Norris and others consider it a form of granulosa-cell tumor. Similar if not identical cells occur in tumors undoubtedly granulosal in nature. Greenhill and Greenblatt think that their case, with typical trabecular granulosa-cell tumor combined with fibromatous areas rich in lipoid, is a connecting link between the "folliculome lipidique" of Lecène, which is now thought to be a luteinized granulosa-cell tumor, and the theca-cell tumor of Loeffler and Priesel. Geist, Gaines and Pollack interpret Greenhill and Greenblatt's case as illustrating bilateral development from a common stem cell. Delarue and Isidor point out that, basically the same, the luteoma is cellular and the thecoma fibrous. Traut, Kuder and Cadden postulate that the granulosa-cell tumor as it matures may undergo luteinization, ischemic necrosis and "collagenous degeneration" followed by fibrosis. In tumors composed principally of theca-like cells the fibrosis is regarded as the sequel of luteinization. It seems probable that the theca-cell tumor is a form of granulosa-cell tumor, but its independent origin cannot be denied.

The *arrhenoblastoma* is a type of so-called masculinizing tumor. It is a disease of younger women. Of 29 cases collected by von Száthmary (1934), 19 were less than 30 years of age and only 2 over 50 years of age, although Young is said to have observed

one at 76 years. Norris states that the highest incidence is in the third and fourth decades. It is an infrequent tumor; Novak in 1938 found reports of only 51 cases, including 11 of his own. The patient presents signs and symptoms much like those of Cushing's syndrome and of adrenal cortical tumors, except that the occurrence of hypertension, hyperglycemia and glycosuria is inconstant and not permanent. Amenorrhea, hirsutism, frontal baldness, low-pitched voice and large larynx, enlargement of clitoris, abnormal deposits of fat or loss of weight, acne, heavy musculature, male appearance of face and figure, and in some advanced cases loss of heterosexual libido, have been observed. Removal of the tumor has resulted in reestablishment of function in the remaining ovary, and subsequent pregnancy has been reported.

The arrhenoblastoma is almost always unilateral, but the number of cases reported does not permit a valid statistical statement as to which side is the more often affected. The tumor is of moderate size, with a smooth capsule, and frequently a nodular outline. The cross section shows multiple nodules, a little more pink in color and softer than the intervening gray material. There is little disposition to hemorrhage and necrosis, but these may occur and a few of the tumors have been cystic. Meyer describes three microscopic varieties. One is the testicular tubular adenoma, which Norris thinks belongs in a separate category; an opinion with which most disagree. In this form there are tubules or acini, surrounded by a limiting fibrous tissue and lined by a single or multiple layer of cuboidal or cylindrical cells, the intervening borders of which are poorly defined, giving the impression of a syncytium, like that of the Sertoli cells of the testis. There are usually also long spindle cells arranged in bundles which interlace to form anastomosing trabeculae. The second microscopic form shows short spindle cells in so-called sarcomatoid arrangement, but even here cuboidal and cylindrical cells in nests or tubules are found. The third form is a combination of the other two. Bang and certain others accept the idea that these tumors contain cells which are prototypes of the interstitial cells of Leydig, but this has not been indisputably

demonstrated. Tumors occur without these large lipoid-containing cells and yet are masculinizing. Furthermore it is not even established beyond question that in the mature testis these cells are responsible for the production of male hormone. Chemical and histo-chemical studies have not given real information and the nature of these cells is still uncertain.

Manifestations of masculinization are most frequent with the sarcomatoid form, least so with the testicular tubular adenoma and in an intermediate position with the combined form.

Because of the small number of cases on record, the degree of malignancy of this tumor has not been determined. Taylor, Wolfermann and Krock say it is predominantly malignant, but Novak thinks it somewhat less likely to be malignant than is true of the granulosa-cell tumor. Krock's patient was relieved by operation but died of recurrence. Von Száthmary's patient was relieved, but masculinization reappeared with recurrence. Both Novak and Norris think of the tumor as carcinoma, but the same argument as regards nomenclature applies here as in connection with the granulosa-cell tumor. Certainly the microscopic distinction between benign and malignant forms is equally difficult.

The associated changes include atrophy of endometrium, of the uterus, of the breasts, and morphological features indicative of depression of the opposite ovary. Norris, in his study of postmortem material, found no significant changes in thyroid, parathyroids, and pineal, but observed degranulation and hyalinization of the basophiles of the pituitary as well as hypertrophy of the acidophile and pale cells of the adrenal cortex. This case then can be included as one of pituitary basophilism.

It is generally agreed that the granulosa-cell tumor and the arrhenoblastoma are different entities. Certain cases of granulosa-cell tumor are accompanied by some manifestations of masculinization, more particularly the thecomas. It is true also that microscopically undifferentiated fields of both types of tumor are practically indistinguishable, but the tumors as a whole have characteristic features. It should be noted, however, that Bergstrand holds it impossible to make a distinction histologically

between the luteinized granulosa-cell tumor and the arrhenoblastoma.

Whether or not the so-called *hypernephroid tumor* of the ovary

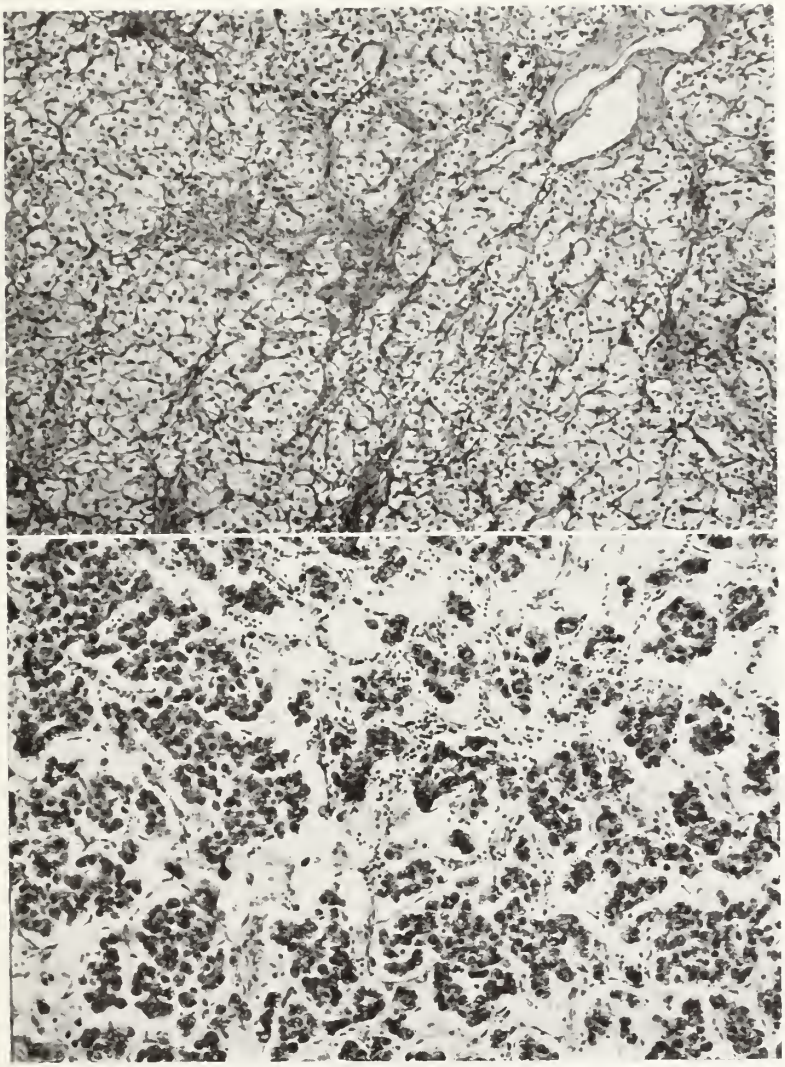


Fig. 7

Fig. 8

Fig. 7. "Hypernephroid" or adrenal tumor of ovary.

Fig. 8. Dysgerminoma. The clusters of large cells are separated by a delicate stroma fairly rich in lymphocytes.

is an entity is thought by some to be doubtful. The very name is an indication of the confusion. Certainly a tumor occurs in the ovary which looks like the cortical adrenal adenoma and it is frequently but not invariably (Glynn) associated with masculinization. Similar lesions may be found in other pelvic tissues, as for example, Van Kirk and Edwards' case in the broad ligament. The tumor has been reported at ages from $3\frac{1}{2}$ to as high as 76 years (Young's case), although it is more common in the later age periods. Its infrequency is shown by the fact that Van Kirk and Edwards found reports of only 27 cases, some of which are not positively identified as primary in the ovary. It is usually unilateral, and varies greatly as to size, occasionally being large. It is usually solid, but may be cystic, is often soft and of yellow color, and as in the renal tumor often shows necrosis and hemorrhage. Microscopically, the cells are large, vacuolated, with definite cell outline, and nuclei which may be round or indented and sometimes vacuolated. The arrangement often suggests that of the zona fasciculata, or even the zona glomerulosa of the adrenal cortex. The cells contain lipids and glycogen, as demonstrated microchemically by Downes and Knox. Chemical analysis shows the presence of phospholipids and cholesterol. Extraction from less than a gram of tumor by Greenblatt, Greenhill and Brown yielded a higher percentage of phospholipid and cholesterol than was true of the other incretory tumors, but the amount of material used raises a question as to the validity of these results. They also found lipoid crystals, the nature of which was not established. However, the lipids of the human adrenal have not been precisely determined quantitatively and until that is done, no satisfactory comparison can be made between the tumor and the gland.

Nevertheless, the cells of the thecoma are large and contain lipids. In some of these so-called hypernephroid tumors, the cells individually or in small groups are surrounded by reticulum, unlike adrenal cortex or cortical adenoma and like theca interna and thecoma. Turnbull has set up a scheme of distinctions between ectopic adrenal, cortical adenoma and corpus luteum, but this can have only little use in differentiation of these neoplasms

of the ovary. Chemically, within the limitations indicated above, the cells seem to be more like those of adrenal cortex than luteinized cells. Thus, both morphologically and chemically, there appears to be a tumor derived from cells of the same order as those of adrenal cortex. If this be true, hypernephroid is a misnomer. The tumors are morphologically and functionally the same as the adrenal cortical adenoma, and that term or something such as interrenaloma should be employed. Undoubtedly there will continue to be difficulty in separating this tumor from luteoma and thecoma. In Rottino and McGrath's report, cases are included which do not properly belong to the group. They found fat but neither glycogen nor fuchsinophile granules, and seem doubtful as to the nature of their case, as implied in the proposed name, masculinovoblastoma.

It is probable that most of these tumors are benign, as is true of comparable lesions in the adrenal. Van Kirk and Edwards report recurrence or metastases in 5 cases, but autopsies were not performed in all and the point of origin not positively identified. In Stadiem's case, for example, the tumor of the ovary, definitely metastatic, looked like those described as primary in the ovary.

The *dysgerminoma* of the ovary is morphologically analogous to the embryonal carcinoma (seminoma) of the testis. The dysgerminoma occurs in earlier life than the embryonal carcinoma of the testis, usually at 30 years or less. Fein and Goldberg's patient was only 2 years old. The ovarian tumor is less than one-third as frequent as the testicular tumor. Seegar's review of 79 cases shows 48 per cent in the right ovary, 26 per cent in the left ovary, and 26 per cent bilateral. The predilection for the right ovary, which in mammals develops more slowly than its fellow and in birds remains undeveloped, is of interest, but would be significant only if it were universal. The tumor is firm and elastic, usually well encapsulated, although local infiltration is not rare, and may occasionally attain great size. Microscopically, it shows more or less alveolated masses of large round cells ("like caviar"!) with focal collections of lymphocytes, similar to the embryonal carcinoma with lymphoid stroma observed in the testis.

Of Meyer's 48 cases, 27 were in women who showed some degree of pseudo-hermaphroditism, much more often than in Seegar's statistics. From the opposite point of view, Schiller states that the dysgerminoma is the most frequent tumor of hermaphroditic gonads. Ordinarily the tumor shows no noteworthy endocrine effects, but Gough reports an instance in a girl $15\frac{1}{2}$ years old with what he calls masculinization. The fact that there was little improvement postoperatively indicates that some other factor was responsible for the virilism. Nevertheless, associated changes may include hypoplasia of the breast, infantile uterus and under-development of external genitalia (Greenblatt and Pund).

It has been generally thought that this tumor has a low incidence of malignancy. Seegar, for example, reported only 3 cases in the 79 he reviewed. As the lesion is further investigated, however, malignancy is more often observed. Greenblatt and Pund found all of their 5 cases to be malignant and Novak and Gray report that 6 of their 17 patients showed either local infiltration or metastasis. Dockerty found an incidence of 45 per cent.

The *Brenner tumor* was called by him *oophoroma folliculare*. Others have named it *fibroma ovarii adenocysticum* and *fibroepithelioma mucinosum benignum*. Timmerberg (1939) collected 139 cases and Smith and Pettit (1939) have added 10 more. Novak and Jones (1939) found 122 cases. It occurs most often after 50 years of age and is uncommon before the twentieth year, but Christidis, Stoïa and Stanciulesco quote Meyer as having observed one in a child of 9 months. Occasionally it is intraligamentary. There are two forms, solid and cystic. The solid form resembles a fibromyoma, but microscopically it is mainly fibrous tissue with solid islands of cells, which appear to be epithelial, or tiny cysts whose lining cells may be goblet cells. There is usually a concentric lamination of the connective tissue about these islands. Smooth muscle has also been reported. It is possible that the microcysts may become large, but the cystic forms are usually in association with pseudomucinous cystadenoma or rarely with serous cystadenoma as pointed out by R. Meyer, Kleine and others. Bland and Goldstein report

one case of malignancy, that of M. Voigt. This was published 4 years before Brenner's paper and the description is more like that of adenocarcinoma than of Brenner tumor. There is no satisfactory evidence of malignancy and no convincing evidence of endocrine effects.

GENESIS OF THE TUMORS

The genesis of these various tumors has been the subject of much dispute. The problem resolves itself basically about two questions. The first is as to whether neoplasms can develop from mature differentiated cells or whether some degree of reversion toward embryonal types, the so-called dedifferentiation, is required. Ancillary to that is the matter of origin of tumors from misplaced embryonal cells in the sense of the Cohnheim theory. The second question concerns the exact embryogenesis of the various cellular constituents of the ovary.

There is some experimental evidence that indicates the origin of tumors from mature differentiated cells, but the general opinion is to the effect that in man, neoplasms develop only from immature, or partially differentiated cells, or from cells which have reverted toward embryonal types. Although it is probable that the Cohnheim theory does not apply to all tumors, it is practically certain that some are satisfactorily explained on that basis. It is reasonable to assume that cells, through heredity or otherwise, come to possess an intrinsic factor which prepares them for unlimited and unrestrained growth; a realization factor brings about neoplasia. The intimate nature of these factors is unknown. It is well established in the experimental animal that endocrine influences may lead to tumor growth in breast and uterus, and perhaps also in pituitary and other ductless glands. Insofar as ovarian tumors are concerned, there is no evidence that points conclusively to any carcinogenic activity by hormones, although Schiller claims to have produced a granulosa-cell tumor by the use of anterior pituitary hormone and a carcinogenic hydrocarbon, but the hormone alone failed.

If Fischel's view be correct, the structures within the ovary, except the ovum, are of mesenchymal origin, but there are those

who adhere to the idea that the surface epithelium, through the supposed Pflüger tubules furnishes the granulosa, and even the ova. The general pathologist cannot resolve these differences of view, but the microscopic character of the tumors is such as to harmonize with the conclusions of Fischel.

R. Meyer's theory as to the origin of the *granulosa-cell tumor* is that it is derived from the nests of granulosa cells, persisting in anovular form in the mature organ. It is pointed out by Schiller and by Geist, Gaines and Pollack that these "granulosa-ballen," although frequent in younger persons, are rare in those age groups where the tumors are most common. Schiller also throws doubt on the likelihood of granulosa persisting for any length of time without the presence of ova, but the dependence of granulosa upon the ovum is still an open question. He also objects to the assumption that neoplasms can arise from cells as mature as those of the granulosa. Te Linde found a granulosa-cell tumor 3 mm. in diameter at the hilum of the ovary of a woman 43 years old and concludes that since follicles do not occur in that situation, the tumor was not derived from granulosa cells. Robinson asserts that the tumor is directly derived from mature granulosa, a view shared, on unconvincing evidence, by Dockerty and MacCarty. Schiller draws attention to the connective tissue character of parts of the tumors and the impossibility of demarcating between essential cells of the tumors and the connective tissue. Upon the basis of Fischel's views, he therefore proposes a unitary theory of genesis. This ascribes the origin of all parts of the tumor to remaining nests of mesenchymal cells, which display their potentialities in neoplastic growth by the production of characteristic granulosa cells and cells like those of connective tissue.

Into this picture are thrown the experiments of Traut and Butterworth, Furth and Butterworth, Butterworth, and Furth and Furth. It was found that irradiation by x-rays in young mice leads to the production of tumors of the ovary 15 times as often as such tumors naturally occur. These included granulosa-cell tumors, luteinized-cell tumors and tubular adenomata. They appeared after the mice had become senile. The general conclusion is that the tubular adenomata, which are not similar

to the arrhenoblastoma, arise from downgrowths of the surface epithelium and that the granulosa-cell tumors arise as the result of stimulation of follicular granulosa cells and interfollicular spindle cells. The growths may become partially or completely luteinized. Traut and Butterworth favor ultimate origin from mesenchyme, whereas Furth and Butterworth favor germinal epithelium. Geist, Gaines and Pollack have also produced these lesions, although they used doses of 200 r., whereas Furth and his associates used 400 r. They conclude that the tumors are derived from undifferentiated parenchyma. The difference between hyperplasia and neoplasia cannot always be assured. Some of these experimental lesions are large, but none has been invasive and none has metastasized. Furthermore, Geist, Gaines and Pollack were unable in a limited number of experiments to transplant successfully, whereas the natural granulosa-cell tumor of the mouse reported by Strong, Gardner and Hill was readily transplantable. At the present time it cannot be denied that these are tumors, but final and absolute proof is wanting.

The experiments with x-ray naturally raise the question as to whether irradiation of the pelvic region of women may induce formation of granulosa-cell tumors. Schiller reported human granulosa-cell tumors after irradiation, but admits that there was no satisfactory evidence to incriminate the irradiation. Traut, in the discussion of the paper by Traut, Kuder and Cadden, said that four instances had been brought to his attention, but hesitated to attach significance to this, pending accumulation of more material. Scheffey, in the discussion of a paper by Novak and Jones, reported two cases of granulosa-cell tumor which followed, at 10 and 9 years, radium therapy for carcinoma of the cervix. In both, however, the treatment for the carcinoma was more important to the patient than the later development of granulosa-cell tumors.

There is little doubt that the so-called *luteoma* is a granulosa-cell tumor with luteinization, but some still hold that cells already luteinized may give rise to these tumors. It is a strain on the beliefs of the general pathologist to accept the proposition that cells already luteinized can undergo neoplastic proliferation.

If the *theca-cell tumor* is a separate entity it may be thought to

arise from *theca interna* or from the primitive cells which give origin to the theca cells. It seems unlikely that mature theca cells can be directly transformed into neoplasm and much more probable that the tumor is derived from cells of the primitive ovarian parenchyma having the potentiality of development into theca, a supposition generally adopted and now accepted by Geist, Gaines and Pollack. Nevertheless, it is at least possible that this tumor is a derivative of the granulosa-cell tumor, due to secondary changes in the cells, although the distribution of reticulum is against this view.

As concerns the *arrhenoblastoma*, Pick, in discussion of the testicular tubular adenoma, ascribed it to remnants of the testicular tubular anlage in the ovarian parenchyma. R. Meyer goes a step further back into embryonal life and attributes it to undifferentiated cells, not utilized during embryonal development, which retain their male-directed potentialities. He found a tiny tubular adenoma in the hilum of an adult ovary, attached to the rete, which he thought proved his theory. Popoff proposes the idea of a spontaneous reactivation of the medullary cords. Norris sees no good reason for deriving the tumor from any special part of the sex gland and thinks it should be looked upon as a tumor "whose morphological picture more or less corresponds to certain, some or all of the varying structural conditions found in the indifferent stage of the sex gland's development." General opinion favors R. Meyer's conception.

The origin of the *adrenal tumor of the ovary* presupposes that such a tumor exists and is of different nature from the luteinized granulosa-cell tumor and the thecoma. Naturally it is thought that this tumor arises from misplacement into the gonad of cells of the neighboring adrenal anlage. The occurrence of ectopic adrenal tissue is well recognized in man and other animals. Rests of this sort have been clearly identified in regions near the adrenal, in the liver, broad ligament, ovarian ligaments, uterus, spermatic vessels and elsewhere. Hochloff quotes R. Meyer as having found cortical tissue in the hilum of the ovary and Neumann as having found chromaffin tissue. Nelson, in his excellent review, reports cortical tissue in the ovary, in the cortex,

hilum and near cysts. Additional cases are reported by Debeyre and Riche and by Saphir and Parker. In the latter case there was associated virilism. That misplaced adrenal tissue in other situations may become neoplastic is widely accepted. Thus, this tumor of the ovary probably originates from misplaced adrenal cortex or mesenchymal cells destined to produce adrenal cortex. Of interest is the report of Schiller which indicates that mesonephric tissue may also be misplaced in the ovary and give rise to what he calls *mesonephroma ovarii.*

The frequent association of *dysgerminoma* with intersexuality and other manifestations of abnormal development of the genitalia and the fact that it is found in teratoma of the ovary, provide evidence in favor of R. Meyer's theory that this tumor arises from cells of the primitive gonad before they have undergone sexual differentiation, that is, before they have been influenced by the presence of the germ cells. R. Meyer is of the opinion that it does not arise from testicular anlage because it is found in otherwise normal women, but Seegar suspects that this may be the origin because of its occurrence in the testis.

The origin of the *Brenner tumor* is ascribed to Pflüger tubules, to Walthard cell heaps, to the ova-balls which develop prior to differentiation into primordial follicles, and (by Kleine) to remnants of the wolffian body. If Fischel is right, there are no Pflüger tubules in the human ovary. Walthard thought the cell heaps he described arise from the surface epithelium and produce adenoma of the ovary. Brenner was uncertain as to whether the lesion develops from Pflüger tubules or ova-balls. R. Meyer is of the opinion that in the Walthard heaps, which included nests of pavement cells, ciliated epithelium and goblet cells, there are undifferentiated cells, all foreign to the normal structure of the ovary. The primitive cells may differentiate to form the constituents of the Brenner tumor and the not infrequently associated pseudomucinous cystadenomas, as well as the rarely associated serous cysts. Simply stated, this means that the tumor originates in indifferent cells of the Walthard cell heaps. Novak and Jones accept this general idea and assert also, wholly upon morphological grounds, that the Brenner tumor may be

converted into pseudomucinous cystadenoma. This differs only slightly from R. Meyer's view that the cystadenoma is a differentiated part of the Brenner tumor.

It is still possible that all the tumors included in this discussion represent the growth of a teratoma in such fashion that one element develops in excess or to the exclusion of other elements. In the opinion of Ewing, this has been established as concerns many of the testicular tumors and may well be true of ovarian tumors. McLester is a protagonist of this view in reference to his case of arrhenoblastoma.

ENDOCRINE PHENOMENA

A discussion of endocrine phenomena associated with these various tumors is somewhat unsatisfactory because of the gaps still to be filled in the knowledge of the internal secretory functions of the ovary, their interrelations with other ductless glands and the fact that few exact observations have been made in patients who bear the tumors. There are also certain technical limitations in the precise determination of amounts of the various hormones in blood, urine and other tissues and secretions. Furthermore, the endocrine factors of normal menstruation are not fully understood, but the process is apparently due to an interaction of estrin and progesterone rather than to the effect solely of estrin. Abnormalities of uterine bleeding may be due to fluctuations in either or both.

That *granulosa-cell tumors* are associated with effects like those of the estrogenic hormone is indicated by sexual precocity in prepuberal age, phenomena of "rejuvenation" in women past the menopause and the common accompaniment of hyperplasia of the endometrium. It is noteworthy, however, that in childhood the menstrual flow has not the regular time and rhythm of the normal menarche, even although breasts are enlarged and bodily conformation together with psychic manifestations may be like those of puberty. In women past the menopause, the flow usually has not the regularity of natural menstrual cycle and may be continuous. The hyperplasia of the endometrium is more often of cystic type than that observed in the normal cycle.

Studies have not yet been made to correlate the kind of hyperplasia with the character of the bleeding. These phenomena are not hyperfeminization nor are they of necessity hyperestrinism. They are abnormal manifestations related to production of estrin and progesterone, often irregular, and resembling rather than duplicating the usual ebb and flow in sexual life. Even protracted bleeding is no proof of excess of estrin, because experimentally the administration continuously rather than intermittently of small amounts of estrogenic substances may induce the endometrial changes (Burch et al.). Corner has also studied the matter of abnormal bleeding. He found that in castrate monkeys a sudden discontinuance of treatment with either estrogens or progesterone results in menstruation-like bleeding. "When the estrogen and progesterone are given simultaneously in suitable amounts, bleeding occurs if the progesterone is discontinued even though sufficient estrogen to prevent bleeding is still being administered." It is suggested that abnormal bleeding is due to deprivation of or imbalance of these hormones, which may lead to various grades of disturbance, including severe metrorrhagia.

Unfortunately, relatively few titrations of estrogens have been made in patients with these tumors. Schuschania, with 5-day collections of urine and feces from a 67 year old woman, found 326 and 619 mouse units of estrogenic substance respectively. Similar tests beginning 66 days after operation were negative. Pratt points out that these quantities are much less than would be expected in pregnancy and that a cyst was removed with the other ovary, the nature of which was not clear, but she suggests that it might have produced the estrin. She says that "interesting as the experiments are, they do not prove the production of oestrin by a granulosa-cell tumor." Frank found estrogenic substance in children with various ovarian tumors. Neumann reported positive results in patients of 46 and 61 years and negative results after operation. Thornton found estrogens in the urine of a woman 53 years old 24 hours after operation. Bland and Goldstein report a positive test in a child 7 years old before operation and a negative result 7 days after operation. When

the tumor recurred 2½ years later, the results were positive again and negative after operation. Huber had a positive result from the urine of a woman 67 years old. Especially impressive is the fact that Gross's 13 months old patient excreted as much as 17,500 international units of estrin per 24-hour specimen of urine, with a return to normal after operation. Tumor or tumor extracts have given positive results in the hands of Eastlake,* Schuschania, R. Meyer, Neumann, and others, but the results are of little value from the quantitative point of view. Gospe, however, found 32 mouse units of estrogenic hormone per gram of fresh tumor tissue, strikingly in excess of the normal content of ovary and far in excess of that reported by Schuschania. Whether this represents production in excess or storage is not yet settled.

Of especial importance are the observations of Strong, Gardner and Hill of a transplantable granulosa-cell tumor of the mouse. In female hosts of the transplants there was continued estrus which disappeared after removal of the tumors. In male mice there was growth of the rudimentary mammary glands like that resulting from ovarian grafts or administration of optimal amounts of estrogenic hormone. Thus it may be said that granulosa-cell tumors produce estrogenic substance, but as to the continuity, or rhythm, or amount, no conclusion can be reached. Thus, it cannot be said whether the condition is due to hyperestrinism or dysestrinism.

In the time of sexual maturity there may be menorrhagia, metrorrhagia, or amenorrhea. The first two have been discussed above. Various explanations are offered for the amenorrhea. Novak suggests that it may be due to the activity of progesterone, and this may well be of importance in the luteinized tumors. Allen found that in monkeys a constant excess of estrogenic hormone causes hyperplasia of the endometrium but does not cause bleeding until the hormone is withdrawn. Hammar quotes Zondek as having shown that the proliferation hinders loosening of the endometrium and thus leads to amenorrhea, but if necrosis occurs, bleeding ensues. Various authors have sug-

* Although the tumor reported by Eastlake was thought to be a sarcoma, Novak (1933) diagnosed it as granulosa-cell tumor and states that R. Meyer agreed.

gested some vague imbalance between ovary and pituitary, principally in the direction of depression of gonadotropic activity upon one ovary as the result of excessive or prolonged production of estrin by the diseased ovary. Allen, Hisaw and Gardner report that the ovary may produce male sex hormone, but it is unlikely that this has any bearing upon the amenorrhea of granulosa-cell and lutein tumors.

Enlargement of the breasts is presumably due to the effects of estrin, either directly or through the intermediation of the pituitary (Gomez and Turner). It is said that colostrum may be produced. The observations of Strong, Gardner and Hill on their transplantable tumor of the mouse and of Gardner, Strong and Smith on a natural granulosa-cell tumor of a mouse show clearly the stimulating effects upon the mammary gland.

It might be assumed that the continuous presence of estrin would have some depressant effect upon the pituitary, but exactly in what manner is uncertain. The production of colostrum (Bang) might be due to a lactogenic hormone and thus produce evidence against depression of that particular function. In occasional instances the Ascheim-Zondek and Friedman tests have been positive; again not a sign of depression. Of course, positive Ascheim-Zondek test might be expected in women past the menopause, as is probably true of Neumann's cases, but in Bland and Goldstein's patient, 7 years of age, it was positive, which naturally suggests that the granulosa-cell tumor may have been responsible.* If the pituitary were depressed, sterility should be expected and this is the rule, but M. Schulze speaks of two cases of granulosa-cell tumor complicating pregnancy and it is hardly possible that the tumors could have arisen after conception. In one case the tumor was removed and pregnancy completed. In only one instance has the pituitary been studied at autopsy; Pratt quotes Kleine as having found no change.

Masculinization, slight or moderate in degree, may accompany

* Positive Ascheim-Zondek tests have been reported in two cases of precocious puberty associated with teratoid tumors of the ovary which contained chorionepitheliomoid tissue, given the suffix "oid" to distinguish this lesion from the tumor of the same nature arising in trophoblast (Fasold; Siegmund).

the amenorrhea of occasional patients with granulosa-cell tumor, especially the luteinized forms. That this is due to male sex-hormone is doubtful, especially since it has been shown by Greene, Burrill and Ivy, and others, that progesterone itself is androgenic and that this activity does not depend upon testis hormone. Maleness may then be due to progesterone itself. Amenorrhea may possibly be due to the depressing action of progesterone upon estrin. Pratt is of the opinion that the virilism is not explained and thinks that in some instances the tumor may have been an arrhenoblastoma. J. Novak and Wallis report a case of what appears to be a luteinized granulosa-cell tumor with masculinization, polycythemia, hypertension and hyperglycemia. There was no estrogenic substance in the blood, nor did the tumor contain androgenic or estrogenic substances. Five weeks after operation estrogenic hormone was found in normal amounts in the urine. It is evident that much more extensive and exact studies are required for the solution of the problem.

Theca-cell tumors, even when luteinized, are more likely to be associated with bleeding than otherwise, and are often accompanied by hyperplasia of the endometrium (Brosig). This is in harmony with the fact that theca cells naturally produce estrin. Varangot calls attention to the fact that whereas granulosa is avascular, the *theca interna* is well vascularized and morphologically resembles a gland of internal secretion that can pour estrogenic hormone into the blood. The tumors are also well vascularized in their more cellular portions. Geist and Spielman found 48 mouse units of estrogen in 32 grams of a thecoma, an amount that more than equals that in the placenta, but although this patient had been bleeding, she suffered from amenorrhea at the time of operation. Novak and Brawner quote Plate as assuming that amenorrhea in this general order of tumor is due to lipoidal change in the tumor cells similar to that in the persistent corpus luteum cysts that may be accompanied by pseudopregnancy. Nevertheless it can generally be said that there is no close correlation between cell form and functional disturbance in the sense just indicated.

Except for the observation in the mouse by Gardner, Strong

and Smith, there is no indication that granulosa-cell tumors lead to carcinoma of the breast. The association of neoplastic disease in the other genital organs cannot definitely be attributed to ovarian tumors. The lesions which may accompany the granulosa-cell tumor have been noted in discussion of the morphology, but it is a far cry to attribute to this association any causal connection. Even the occasional reports of the association of carcinoma with hyperplasia of the endometrium cannot be given much weight unless it can be shown that the incidence is higher with granulosa-cell tumor than in comparable age groups without.

The *arrhenoblastoma* is looked upon as a typical masculinizing tumor. Taking the group as a whole and with particular attention to the usual lack of sexual change in association with the tubular testicular adenoma, there are certainly instances, relatively frequent, without accompanying masculinization. Even when virilism does occur, it has not been conclusively demonstrated to be due to male sex hormone, even although that appears likely. Experimental studies of endocrines force abandonment of the monhormonic theory of sex. Furthermore, as shown by Ivy, Greene and Burrill, and others, sex determination is not solely due to the germ cell, but is brought about in part by endocrines. Thus, injections of estrogens into pregnant rats led to feminization of the male offspring and similar injections of male hormones led to masculinization of the female offspring. These and many other observations support the dihormonic theory. Both human sexes may have both male and female sex hormones and the mere presence of male hormone in a woman may be of no significance. The observation of von Száthmary upon a 25 year old woman with arrhenoblastoma and associated amenorrhea and masculinization showed that before operation there was neither estrogenic substance nor "androkinin," but that a small amount of estrogens was demonstrated postoperatively. This simply shows depression of production of estrin and does not explain the mechanism. Of interest is the fact that the patient was much improved and menstruated, but with recurrence she again had amenorrhea and became masculinized. At this time the urine contained androgenic but no estrogenic

substance and the recurrent mass was devoid of estrogens. The masculinization began to disappear but reappeared with subsequent recurrence. Several weeks before death the urine showed estrogens and decreased androgenic substance which von Száthmary explains as due to a sarcomatous change in the character of the tumor. Norris's report of autopsy upon a patient with malignant arrhenoblastoma shows changes in other endocrines like those induced experimentally by androgens. In spite of the lack of convincing evidence, it is probable that the arrhenoblastoma produces androgenic substance and that the depression of ovaries and breasts is the result of suppression of estrin; further, that the other features such as beard, general hirsutism, male conformation, enlarged larynx and clitoris are due to male sex hormone. The influence upon the pituitary is further indicated by the occasional presence of hypertension, hyperglycemia and glycosuria. That the changes are not irreversible is indicated by numerous reports of loss of masculinization. Indeed Strassmann reports a patient who subsequently became pregnant. In passing, the case of Krönke may be quoted, in which there was a teratoma of the ovary accompanied by Cushing's syndrome. Tissue like pituitary was found but there is no note as to basophilism in this mass.

Although after operation there is much improvement, hirsutism is likely to persist in some degree. This has been attributed to permanent change in the pituitary, but it is more likely the result of a somatic alteration in the hair follicles, only partially if at all reversible.

Much remains in the way of clarification of the problem, especially in exact studies of the patient. Maleness and femaleness are somewhat relative and depend on family traits and racial stocks. Darker racial stocks and families are likely to be somewhat more hairy than those of lighter complexion. This fact is not always given proper consideration in the evaluation of lesser degrees of hirsutism. Even in certain families of blonds, hairiness may occur. Thus it is essential to know the racial stock, the family peculiarities and the previous state of the patient, before a conclusion is justified. The hormones should be pre-

cisely titrated. The pathologist should make further studies of the cells in the tumor which have some resemblance to the interstitial cells of Leydig.

The *adrenal tumor* of the ovary, as well as adrenal rests in that organ, may also be masculinizing. Glynn is of the opinion that this is not to be correlated with morphology, since tumors identical in appearance may in one case be masculinizing and in another not. The interrelation between adrenal and sex is generally recognized, but not in all its details. Rosset found that in a woman 36 years old, with malignant adrenal tumor, the ovaries were both functionally and morphologically depressed. Schiller, in his discussion of Rottino and McGrath's paper, accepts the Bauer hypothesis that adrenal tumors have a tendency to support characters of the opposite sex and may masculinize the female or feminize the male. He states that he has seen two instances of structures like adrenal in the testis associated with feminization. There is no doubt that adrenal tumors may bring about precocious puberty of boys and girls, that they masculinize women and feminize men. Broster and Vines speak of fuchsinophile cells which they believe to be the masculinizing elements of adrenal lesions, but except for Rottino and McGrath's failure to demonstrate them in their ovarian tumor, they are not otherwise mentioned in this connection. The similarity of the cells of corpus luteum and those of adrenal cortex has led to some confusion. Mulon's studies of the lipoids of adrenal, corpus luteum and interstitial cells of the testis are quoted as pointing to their chemical similarity or identity, but his examinations are based upon microchemical studies of doubtful dependability, as indicated by Hoerr. More important is the observation that pregnant animals survive adrenalectomy longer than do others, which may well be due to the presence of corpus luteum. These and other facts indicate the difficulty of distinction, as to form and function, between thecoma and adrenal tumor of the ovary.

As stated above, progesterone derived from corpus luteum may be masculinizing and so is the androgenic substance (or substances) from adrenal cortex. In Saphir and Parker's case of adrenal inclusion in the ovary, estrogenic substance was present

in large amounts, but the ovaries were morphologically depressed. Crooke and Callow are doubtful that adrenal cortical tumors of the female are ever associated with increase of estrogens. There is no question of the fact that such tumors in the male, accompanied by feminization and impotence, may be associated with markedly increased output of estrogens in the urine. Extracts of the adrenal cortical tumor, reported by Rosset, had no effect upon the sexual cycle of rats. In the discussion above of granulosa-cell tumors, the suggestion was offered that dysfunction may be significant in contrast to over- or under-function. That this may be important in adrenal cortical tumors is indicated by the isolation from the urine of a man with malignant adrenal tumor, by Burrows and his associates, of an androgenic substance not naturally present in urine. Thus, there is work ahead for clinician and endocrinologist. The pathologist must determine chemically the lipid content of these lesions; he must elucidate further the meaning of fuchsinophile cells in the adrenal cortical tumors and determine whether or not they occur in the ovarian neoplasm.

No clear-cut hormonal disturbances are associated with the *dysgerminoma.* Intersexuality is a concomitant as are hypoplasia of uterus and external genitalia. In many instances, however, no such phenomena are observed. Thus, relations of cause and effect are entirely obscure. The production of gonadotropic hormones when comparable tumors are present in the testis is well known. Except for Fauvet's case and very few others, such determinations have not been made in connection with the ovarian tumor and, as Seegar points out, there is nothing to indicate that they are present in amounts in excess of those found in castrates or in the menopause. Furthermore, there are no morphological studies of the pituitary. Gough's report of a $15\frac{1}{2}$ year old girl, who was said to have been masculinized, shows that the removal of a large dysgerminoma failed to produce significant change in the patient. Thus, there is no solid ground for assuming that the tumor was the cause of the masculinity.

Since the *Brenner tumor* is usually seen in older women, it would not be surprising to discover gonadotropic substances in

blood and urine, but this would probably be because of the atrophic ovaries. There is no reason for believing that this tumor is functionally active.

Epicrisis. This review covers what is actually known of the group of ovarian tumors which may produce sexual hormonal disturbances. Typical forms are usually recognized with little difficulty upon gross anatomical and microscopic features. In these instances information as to hormonal activity is merely ancillary and it is found that some tumors are active and others in the same morphological group inactive. In morphological variants, a knowledge of the function may aid materially in the diagnosis. Thus, in certain cases the diagnosis, as is true in other fields, is clinico-pathological. Even so, confusing forms are not rare. It is not true that these tumors can be identified only if they are functionally active. It is unfortunate that so many of the observations of functional change are upon individual cases. This has meant diversity of methods and reports, often difficult or impossible to compare with one another. To be sure, endocrinological methods are being better standardized and this holds promise for the future in the field of ovarian tumors. It must also be recognized that endocrine dysfunction in man is subject to variations that do not prevail in the experimental animal. Complete understanding can only result from comprehensive functional and morphological studies of all cases as they come under observation.

REFERENCES

Allen, E., Hisaw, F. L., and Gardner, W. U., *in* Allen, E., Danforth, C. H., and Doisy, E. A.: Sex and Internal Secretions, Ed. 2, Baltimore, Williams & Wilkins, 1939, p. 452.

Bang, F.: Endocrine tumours of testis and ovary, Acta path. et microbiol. Scandinav., Suppl. **38**, p. 91, 1938.

Bergstrand, H.: Ueber die Natur der virilisierenden Ovarialtumoren, Acta path. et microbiol. Scandinav., Suppl. **16**, p. 31, 1933.

Bergstrand, H.: Luteinisierung der Ovarien bei einem Falle von basophilem Hypophysenadenom mit Cushings Symptomenkomplex, Virchows Arch. f. path. Anat., **293**: 413, 1934.

Bergstrand, H.: Discussion of paper by Bang, v.s.

Bland, P. B., and Goldstein, L.: Granulosa cell tumor of the ovary in a child with precocity, Am. J. Obst. & Gynec., **28**: 596, 1934.

Bland, P. B., and Goldstein, L.: Granulosa cell and Brenner tumors of the ovary, Surg., Gynec. & Obst., **61**: 250, 1935.

Brenner, F.: Das Oophoroma folliculare, Frankf. Ztschr. f. Path., **1**: 150, 1907.

Brosig, W.: Zur Frage der luteinisierten Thecazelltumoren (Fibroma thecocellulare xanthomatodes ovarii Loeffler-Priesel), Frankf. Ztschr. f. Path., **49**: 376, 1936.

Broster, L. R., and Vines, H. W. C.: The Adrenal Cortex: A Surgical and Pathological Study, London, H. K. Lewis & Co. Ltd., 1933.

Burch, J. C., McClellan, G. S., Johnson, C. D., and Ellison, E. T.: The diagnosis and classification of menstrual disorders, J. A. M. A., **108**: 96, 1937.

Burch, J. C., Phelps, D., and Wolfe, J. M.: Endometrial hyperplasia, Arch. Path., **17**: 799, 1934.

Burrows, H., Cook, J. W., Roe, E. M. F., and Warren, F. L.: Isolation of $\Delta^{3:5}$-androstadiene-17-one from the urine of a man with a malignant tumour of the adrenal cortex, Biochem. J., **31**: 950, 1937; see also Callow, N. H., Callow, R. K., and Emmens, C. W.: ibid., **32**: 1312, 1938.

Butterworth, J. S.: Observations on the histogenesis of ovarian tumors produced in mice by x-rays, Am. J. Cancer, **31**: 85, 1937.

Christidis, E., Stoïa and Stanciulesco, P.: Tumeur ovarienne du type Brenner, Bull. Assoc. franç. p. l'étude du cancer, **26**: 663, 1937.

Collins, C. G., Varino, G., and Weed, J. C.: Theca cell tumors of the ovary, J. A. M. A., **113**: 1634, 1939.

Compton, B. C.: Malignancy of granulosa cell tumors, with report of one case with recurrence after sixteen years, Am. J. Obst. & Gynec., **34**: 85, 1937.

Corner, G. W.: The ovarian hormones and experimental menstruation, Am. J. Obst. & Gynec., **38**: 862, 1939.

Cosacesco, A., Draganesco, St., Georgesco, M., and Dinischiotu, G. T.: Lutéinome de l'ovaire: Contribution anatomo-clinique à l'étude du virilisme ovarien, Presse méd., **39**: 1264, 1931.

Crooke, A. C., and Callow, R. K.: The differential diagnosis of forms of basophilism (Cushing's syndrome), particularly by the estimation of urinary androgens, Quart. J. Med., **8**: 233, 1939.

Debeyre, A., and Riche, O.: Surrénale accessoire dans l'ovaire, Compt. rend. Soc. de biol., **63**: 733, 1907.

Delarue, J., and Isidor, P.: Sur deux cas de tumeur lipidique de l'ovaire: Tumeur à type de luteinome et tumeur à type thécale, Bull. Assoc. franç. p. l'étude du cancer, **27**: 429, 1938.

Dockerty, M. B.: Dysgerminoma, Proc. Staff Meet., Mayo Clinic, **14**: 545, 1939.

Dockerty, M. B., and MacCarty, W. C.: Arrhenoblastoma, Surg., Gynec. & Obst., **68**: 767, 1939.

Dockerty, M. B., and MacCarty, W. C.: Granulosa cell tumors, with the report of a 34 pound specimen and a review, Am. J. Obst. & Gynec., **37**: 425, 1939.

Dockerty, M. B., and MacCarty, W. C.: Granulosa cell neoplasm with a discussion of possible histogenesis, Am. J. Obst. & Gynec., **38:** 698, 1939.

Downes, W. A., and Knox, L. C.: Hypernephroma of the ovary. Report of a case in a child three and one-half years of age, J. A. M. A., **82:** 1315, 1924.

Dudman, V. E.: Disgerminoma and arrhenoblastoma, West. J. Surg., **47:** 128, 1939.

Eastlake, C.: Pubertas precox: Report of a case of proved etiology, Colorado Med., **28:** 404, 1931.

Fasold, H.: Ein Teratom des Ovars mit chorionepitheliomähnlichen Metastasen als Ursache einer Pubertas praecox, mit positiver Schwangerschaftsreaktion, Ztschr. f. Kinderh., **51:** 519, 1931.

Fauvet, E.: Zur Klinik des Disgerminoms, Zentralbl. f. Gynäk., **60:** 675, 1936.

Fein, M. J., and Goldberg, R.: Embryonal carcinoma of ovaries, Internat. J. Med. & Surg., **47:** 530, 1934.

Fischel, A.: Ueber die Entwicklung der Keimdrüsen des Menschen, Ztschr. f. Anat. u. Entwicklungsges. (Ztschr. f. d. ges. Anat.), **92:** 34, 1930.

Frank, R. T.: Premature sexual development in children due to malignant ovarian tumors, Am. J. Dis. Child., **43:** 942, 1932.

Furth, J., and Furth, O. B.: Neoplastic diseases produced in mice by general irradiation with x-rays; I. Incidence and types of neoplasms, Am. J. Cancer, **28:** 54, 1936.

Furth, J., and Butterworth, J. S.: Neoplastic diseases occurring among mice subjected to general irradiation with x-rays; II. Ovarian tumors and associated lesions, Am. J. Cancer, **28:** 66, 1936.

Gardner, W. S.: Normal and pathological developments from the cells lining the graafian follicle, Surg., Gyn. & Obst., **67:** 455, 1938.

Gardner, W. U., Strong, L. C., and Smith, G. M.: An observation of primary tumors of the pituitary, ovaries and mammary glands in a mouse, Am. J. Cancer, **26:** 541, 1936.

Geist, S. H.: Theca cell tumors, Am. J. Obst. & Gynec., **30:** 480, 1935.

Geist, S. H.: The histogenesis of certain ovarian tumors and their biologic effects, Am. J. Obst. & Gynec., **30:** 650, 1935.

Geist, S. H., and Gaines, J. A.: Theca cell tumors, Am. J. Obst. & Gynec., **35:** 39, 1938.

Geist, S. H., Gaines, J. A., and Pollack, A. D.: Experimental biologically active ovarian tumors in mice. Histogenesis and relationship to similar human ovarian tumors, Am. J. Obst. & Gynec., **38:** 786, 1939.

Geist, S. H., and Spielman, F.: An unusual ovarian tumor containing an estrogenic hormone, J. A. M. A., **104:** 2173, 1935.

Glynn, E. E.: The adrenal cortex, its rests and tumours; its relation to other ductless glands, and especially to sex, Quart. J. Med., **5:** 157, 1911–12.

Gomez, E. T., and Turner, C. W.: The effect of anol on the growth of the mammary gland, Am. J. Cancer, **37:** 108, 1939.

Gospe, S. M.: Bio-assay of a granulosa cell tumor, Am. J. Obst. & Gynec., **32:** 495, 1936.

Gough, A.: A case of disgerminoma of the ovary associated with masculinity, J. Obst. & Gynaec. Brit. Emp., **45**: 799, 1938.

Greenblatt, R. B., Greenhill, J. P., and Brown, W. R.: Variations of lipoid content in certain ovarian tumors, Am. J. Obst. & Gynec., **37**: 929, 1939.

Greenblatt, R. B., and Pund, E. R.: Disgerminoma ovarii, Am. J. Obst. & Gynec., **35**: 667, 1938.

Greene, R. R., Burrill, M. W., and Ivy, A. C.: Progesterone is androgenic, Endocrinology, **24**: 351, 1939.

Greenhill, J. P., and Greenblatt, R. B.: Status of the thecoma and its relationship to the granulosa cell tumor, Am. J. Obst. & Gynec., **36**: 684, 1938.

Gross, R. E.: A syllabus of neoplasms producing endocrine disturbances in childhood, Am. J. Dis. Child., in press.

Hammar, S.: Ueber Thekazellentumoren aus Anlass eines eigenen Falles, Acta obst. et gynec. Scandinav., **17**: 516, 1937.

Harms, C.: Ueber Granulosazellgeschwülste bei jungen Mädchen, Zentralbl. f. Gynäk., **61**: 17, 1937.

Harvey, W. F., Dawson, E. K., and Innes, J. R. M.: Debatable tumours in human and animal pathology. VII. Granulosa-cell tumour of the ovary, Edinburgh M. J., **46**: 256, 1939.

Hochloff, A. W.: Zur Klinik und pathologischen Anatomie der Ovariumhypernephrome, Arch. f. Gynäk., **136**: 623, 1929.

Hoerr, N. L.: Histological studies on lipins. I. On osmic acid as a microchemical reagent with special reference to lipins, Anat. Record, **66**: 149, 1936; II. A cytological analysis of the liposomes in the adrenal cortex of the guinea pig, ibid., **66**: 317, 1936.

Holland, E., and McHugh, T.: Granulosa-celled tumour of the ovary, South African M. J., **12**: 888, 1938.

Huber, H.: Thecazelltumor als Blutungsursache in der Menopause, Zentralbl. f. Gynäk., **61**: 14, 1937.

Hückel, H.: Ueber die Bösartigkeit von Granulosazelltumoren, Arch. f. Gynäk., **164**: 508, 1937.

Hunt, V. C., and Simon, H. E.: Carcinoma of the ovary in infancy, Ann. Surg., **87**: 84, 1928.

Ivy, A. C., Greene, R. R., and Burrill, M. W.: Intersexuality or pseudohermaphrodism, Ann. Int. Med., **13**: 68, 1939.

v. Kahlden, C.: Ueber eine eigenthümliche Form des Ovarialcarcinoms, Centralbl. f. allg. Path. u. path. Anat., **6**: 257, 1895.

Klaften, E.: Weiterer Beitrag zur Klinik und mikroskopischen Anatomie der Granulosazelltumoren des Eierstockes, Arch. f. Gynäk., **150**: 643, 1932.

Kleine, H. O.: Beiträge zur Klinik des Disgerminoma ovarii, Arch. f. Gynäk., **158**: 89, 1934.

Kleine, H. O.: Zur Klärung der Histogenese der Brennerschen Eierstocksgeschwülste, Ztschr. f. Geburtsh. u. Gynäk., **114**: 125, 1937.

Krönke, E., and Parade, G. W.: Morbus Cushing bei Ovarialteratom, Ztschr. f. klin. Med., **134**: 698, 1938.

Löffler, E., and Priesel, A.: Bindegewebige Gewächse des Eierstockes von besonderer Bauart (Fibroma thecocellulare xanthomatodes ovarii), Beitr. z. path. Anat. u. allg. Path., **90**: 199, 1932.

Löffler, E., and Priesel, A.: Thekazellengewächse des Eierstockes, Wien. med. Wchnschr., **84**: 400, 1934.

McCahey, J. F., and Ramsay, A. J.: Virilism and female pseudo-hermaphroditism with relation to the bisexual nature of the ovary, Am. J. Obst. & Gynec., **36**: 108, 1938.

McLester, J. B.: Arrhenoblastoma: a special type of teratoma. Report of a case, Arch. Int. Med., **57**: 773, 1936.

Melnick, P. J., and Kanter, A. E.: Theca cell tumors of the ovary, Am. J. Obst. & Gynec., **27**: 41, 1934.

Meyer, R.: The pathology of some special ovarian tumors and their relation to sex characteristics, Am. J. Obst. & Gynec., **22**: 697, 1931.

Meyer, R.: Ueber verschiedene Erscheinungsformen der als Typus Brenner bekannten Eierstocksgeschwulst, ihre Absonderung von den Granulosazelltumoren und Zuordnung unter andere Ovarialgeschwülste, Arch. f. Gynäk., **148**: 541, 1932; see also Zentralbl. f. Gynäk., **56**: 770, 1932.

Mulon, P.: Sur certaines cellules des corps jaunes chez le cobaye, Compt. rend. Soc. biol., **58**[1]: 614, 1906.

Nelson, A. A.: Accessory adrenal cortical tissue, Arch. Path., **27**: 955, 1939.

Neumann, H. O.: Granulosazelltumoren als Hormonspender?, Endokrinologie, **12**: 166, 1933.

Noordenbos, W.: Pubertas praecox, Nederl. tijdschr. v. geneesk., **81**: 2288, 1937.

Norris, E. H.: Arrhenoblastoma. A malignant ovarian tumor associated with endocrinological effects, Am. J. Cancer, **32**: 1, 1938.

Norris, E. H.: Granulosa-cell carcinoma. A malignant ovarian tumor associated with endocrinological effects, Am. J. Cancer, **33**: 538, 1938.

Novak, E.: Granulosa cell ovarian tumors as a cause of precocious puberty with a report of 3 cases, Am. J. Obst. & Gynec., **26**: 505, 1933.

Novak, E.: Masculinizing tumors of the ovary (arrhenoblastoma, adrenal ovarian tumors) with report of 6 additional cases of arrhenoblastoma, Am. J. Obst. & Gynec., **36**: 840, 1938.

Novak, E., and Brawner, J. N., Jr.: Granulosa cell tumors of the ovary, Am. J. Obst. & Gynec., **28**: 637, 1934.

Novak, E., and Gray, L. A.: Disgerminoma of the ovary; Clinical and pathological study of seventeen cases, Am. J. Obst. & Gynec., **35**: 925, 1938.

Novak, E., and Jones, H. W.: Brenner tumors of the ovary, Am. J. Obst. & Gynec., **38**: 872, 1939.

Novak, E., and Long, J. H.: Ovarian tumors associated with secondary sex changes, J. A. M. A., **101**: 1057, 1933.

Novak, J., and Wallis, O.: Vermännlichung und Wiederverweiblichung. (Beitrag zur Kenntnis der "Luteinzellentumoren" des Ovariums), Arch. f. Gynäk., **164:** 543, 1937.

Patterson, J. H., and McCullagh, W. M. H.: Case of theca-cell tumour of the ovary in a woman aged ninety-two years, J. Obst. & Gynaec. Brit. Emp., **43:** 1186, 1936.

Plate, W. P.: Eine seltene Form eines Granulosazelltumors des Ovariums, das sog. "Folliculome lipidique" (Lecène), Arch. f. Gynäk., **153:** 318, 1933.

Popoff, N. W.: Testicular tubular adenoma of the ovary. Its etiologic relation to embryonic vestiges and spontaneous sex reversal of the female gonads. Report of a case, Arch. Path., **9:** 31, 1930.

Pratt, F. B.: Granulosa-cell tumours of the ovary; A review of the literature, J. Obst. & Gynaec. Brit. Emp., **44:** 880, 1937.

Robinson, M. R.: Primary and secondary ovarian cancer, Surg., Gynec. & Obst., **51:** 321, 1930.

Rockstroh, H.: Ueber begleitende und über ursächlich bedeutsame Erkrankungen der Adenomyosis uteri interna, insbesondere Fälle von Carcinoma adenomatosum uteri und Fälle von Granulosazelltumor des Ovars mit Adenomyosis uteri interna, Zentralbl. f. Gynäk., **60:** 550, 1936.

Rosset, W.: Malignes Nebennierenrindenadenom und seine hormonale Wirkung auf das Ovar mit Versuchen über den Hormongehalt des Tumors an der weissen Ratte, Ztschr. f. Geburtsh. u. Gynäk., **118:** 273, 1939.

Rottino, A., and McGrath, J. F.: Masculinovoblastoma; Primary masculinizing tumor of the ovary (so-called large cell variety—hypernephroid—luteoma), Arch. Int. Med., **63:** 686, 1939.

Saphir, W., and Parker, M. L.: Adrenal virilism, J. A. M. A., **107:** 1286, 1936.

Scheffey, L. C.: Discussion of paper by Novak and Jones, Am. J. Obst. & Gynec., **38:** 885, 1939.

Schiller, W.: Pathologie und Klinik der Granulosazelltumoren, Vienna, Maudrich, 1934.

Schiller, W.: Recent findings in solid ovarian tumours, J. Obst. & Gynaec. Brit. Emp., **43:** 1135, 1936.

Schiller, W.: Discussion of paper by Rottino and McGrath, v.s.

Schiller, W.: Mesonephroma ovarii, Am. J. Cancer, **35:** 1, 1939.

Schulze, M.: Granulosa cell tumor of the ovary, West. J. Surg., **47:** 114, 1939.

Schuschania, P.: Ergebnisse von Mengenbestimmungen des Sexualhormons; Sexualhormon im Harn und Kot bei, a. Metropathia haemorrhagica juvenilis (glandulär-cystischer Hyperplasie), b. Granulosazelltumor des Ovars mit glandulär-cystischer Hyperplasie des Endometriums, Zentralbl. f. Gynäk., **54:** 1924, 1930.

Seegar, G. E.: Ovarian dysgerminoma, Arch. Surg., **37:** 697, 1938.

Sevringhaus, E. L.: The choice of ovarian or pituitary therapy for menstrual disturbances, Ann. Int. Med., **13:** 629, 1939.

Siegmund, H.: Pubertas praecox als Folge chorionepitheliomatöser Wucherungen, Arch. f. Gynäk., **149:** 498, 1932.

Smith, G. van S., and Pettit, R. D.: Ten cases of Brenner tumor of the ovary, Am. J. Obst., **38:** 156, 1939.

Soltmann, C. H.: Ueber einen ungewöhnlichen Fall von Granulosazellgewächs des Eierstockes mit Knochenmetastasen, Virchows Arch. f. path. Anat., **284:** 466, 1932.

Stadiem, M. L.: An ovarian hypernephroma, Am. J. Surg., **37:** 312, 1937.

Strassmann, E.: Vorführung einer Frau mit Erscheinungen von Vermännlichung durch Ovarialtumor und Wiederverweiblichung durch Operation, Ztschr. f. Geburtsh. u. Gynäk., **98:** 131, 1930.

Strong, L. C., Gardner, W. U., and Hill, R. T.: Production of estrogenic hormone by transplantable ovarian carcinoma, Endocrinology, **21:** 268, 1937.

v. Száthmary, Z.: Ueber eine virilisierende Ovarialgeschwulst (Arrhenoblastoma ovarii), Arch. f. Gynäk., **157:** 170, 1934.

v. Száthmary, Z.: Hormonuntersuchungen bei Arrhenoblastom, Arch. f. Gynäk., **164:** 478, 1937.

Taylor, J. M., Wolfermann, S. J., and Krock, F.: Arrhenoblastoma of the ovary, Surg., Gynec. & Obst., **56:** 1040, 1933.

Te Linde, R. W.: Granulosal-cell tumors of the ovary and their relation to postmenopausal bleeding, Am. J. Obst. & Gynec., **20:** 552, 1930.

Thornton, H. C.: Granulosa-cell tumors of the ovary, with report of a case, Am. J. Cancer, **23:** 522, 1935.

Timmerberg, S.: Ueber Brenner-Tumoren des Ovarium mit 9 neuen Fällen, Ztschr. f. Geburtsh., **119:** 234, 1939.

Traut, H. F., and Butterworth, J. S.: Theca, granulosa, lutein cell tumors of human ovary and similar tumors of mouse's ovary, Am. J. Obst. & Gynec., **34:** 987, 1937.

Traut, H. F., Kuder, A., and Cadden, J. F.: A study of the reticulum and luteinization in granulosa and theca cell tumors of the ovary, Am. J. Obst. & Gynec., **38:** 798, 1939.

Traut, H. F., and Marchetti, A. A.: A study of fifty granulosa and theca cell tumors of the ovary. Report before Third International Cancer Congress, Atlantic City, N. J., Sept., 1939.

Turnbull, H., and Gordon, A. K.: Hypernephroma of the ovary, Brit. M. J., **1:** 133, 1920.

Van Kirk, F. W., Jr., and Edwards, E. A.: Hypernephroma of the ovary, Am. J. Cancer, **37:** 209, 1939.

Varangot, J.: La réaction thécale du stroma dans les tumeurs de la granulosa ovarienne, Bull. Assoc. franç. p. l'étude du cancer, **27:** 440, 1938.

Voigt, M.: Ueber Carcinoma folliculoides ovarii, Arch. f. Gynäk., **70:** 87, 1903.

Voigt, W. W.: Primary giant granulosa cell tumor of retroperitoneal origin with development into the mesosigmoideum, Am. J. Obst. & Gynec., **36:** 688, 1938.

Walthard, M.: Zur Aetiologie der Ovarialadenome, Ztschr. f. Geburtsh. u. Gynäk., **49:** 233, 1903.

Young, A. M.: Pathological changes resulting from excess and deficient secretion of ductless glands, Am. J. Clin. Path., **5:** 180, 1935.

Experiments in the Environmental Control of Epidemic Respiratory Infection*

By W. F. Wells, Joseph Stokes, Jr., M.D., Mildred W. Wells, M.D., and Theodore S. Wilder, M.D.

According to our hypothesis, epidemic contagion may be spread as droplet nuclei expelled and breathed in by the occupants of semi-enclosed spaces. The destruction of droplet nuclei infection by ultra-violet light would, therefore, seem to be a promising means of preventing contagious infections. The effect of lethal irradiation of the air breathed by selected human aggregations is being studied by appropriate epidemiologic techniques. Elimination of droplet nuclei infection exceeds that accomplished by 100 overturns an hour.

In the simplest case it is possible to separate subjects, fixed in position, with physical or ultra-violet light barriers. The design of this type of installation was developed experimentally at the Henry Phipps Institute, from the light barrier installed by Dr. McKhann in the corridor of the isolation unit of the Children's Hospital, Boston, preventing the spread of chicken-pox from one side to the other side of the barrier. Cubicle isolation with light barriers was first installed at the Cradle for new-born infants at

* From the Laboratories for the Study of Air-borne Infection, School of Medicine, University of Pennsylvania. Supported by a grant from the Commonwealth Fund.

A synthesis of papers presented by the authors before the College of Physicians of Philadelphia, Section on Public Health, Preventive and Industrial Medicine, December 4, 1939. W. F. Wells presented his theory of contagion, the culmination of eight years study on air-borne infection, which provided the basis for the experiments here reported; Dr. Stokes described the installations in which a full-scale experimental test of this hypothesis is being conducted; Dr. Mildred W. Wells described the epidemiologic characteristics of the aggregations under study and epidemiologic methods of study; Dr. Wilder discussed the problem as the school physician, during the past eight years, of the Germantown Friends School, whose primary department was chosen as an experimental unit.

Evanston, Illinois. Curtains of light, dropped from the ceiling to the floor, block off the cubicles from the corridor and each other. Light curtains continuous with an ultra-violet light ceiling thrown over the top of cubicle partitions into which they project provide, in the experimental wards of the Children's Hospitals of Philadelphia and Boston, a more generally applicable type.

Curtain isolation is not possible where subjects move freely about in the protected atmosphere, but irradiation of the upper air of the room above the eye level eliminates most micro-organisms expelled as droplet nuclei before they can be breathed by other occupants of the atmosphere. Indirect irradiation of a 24-hour atmosphere in a senile building of the newly finished Marlboro State Hospital, enhanced by a generally diffuse but lethally effective direct irradiation from highly reflecting surfaces, affords considerable protection in the crowded dormitories and day rooms. In the dining room, where the exposure time was short, direct irradiation of the type employed in our operating rooms, is permissible.

Demonstration of protection afforded intermittent aggregations requires independent evidence that infection took place within the atmosphere shared by the temporary aggregation. The incubation period of typical childhood contagions provides evidence needed to connect the infector with the infectee, and the primary department of the Germantown Friends School has been chosen as an experimental unit. Interclass, intradepartmental infection so reduced the difference between total infection in irradiated and unirradiated classrooms that it was decided to irradiate the whole department and compare experience with former records in the primary department and with other departments of the school. Other gathering places, such as gymnasiums, lunch room, and corridors, with brief exposure, permitted the high efficiency of direct irradiation. The shop, with low head room, and the rest rooms required special measures.

Altogether these installations offer unusual opportunities for irradiating atmospheres under living conditions. Their bactericidal efficiency in reducing nuclei infection have been demon-

strated by special techniques. The demonstration of a corresponding reduction in the spread of respiratory infection presents special epidemiologic problems.

It would seem at first sight as though continuous aggregations within an enclosed atmosphere would offer the best epidemiologic field of experiment. The spread of infection can be demonstrated directly and the conditions are, to a large extent, controllable. Upon closer examination, however, it is seen that they are limited in extent and apply only to special groups of the population, such as the very young, the very old, the very sick, or those subjected to compulsory confinement. The types of infection to which the very young and the very old are susceptible further limits the scope of the phenomenon under observation. Consequently a long period will be required for statistically significant data to be collected.

The Cradle has unusual control over the infants under observation and the subjects in the Hospital wards are likewise well controlled. The numbers involved are not large and the number of cross infections is quite limited. At Marlboro the number of subjects is much larger, but no particular control is possible. Greater numbers will, therefore, be necessary for a statistically determinate conclusion. In an orphanage exists the greatest opportunity for the spread of infection by other routes than the air, and a successful demonstration of prevention of contagion spread by irradiation would not only mean the environmental control of air-borne infection but the absence of a significant amount of infection spread by other routes.

Intermittent aggregations seem almost hopeless at first sight. In practice, however, it is possible to select large groups from the population of children susceptible to childhood contagions and readily determine the epidemic spread of these contagions among these aggregations occupying the same atmosphere. Characteristic differences in the spread of epidemic childhood contagion in irradiated and unirradiated school rooms have been observed during the past two years. If such differences are maintained for a sufficient number of years over a broad enough base, both the theory of air-borne infection and its sanitary control can be epidemiologically demonstrated.

Transactions of the College and Its Sections, 1939

The College

January 4. Bauer, Walter. Studies Pertaining to the Origin and Nature of Hypertrophic Arthritis.[1] (*Nathan Lewis Hatfield Lecture XXI.*)

February 1. Long, C. N. H. Diabetes Mellitus in the Light of Our Present Knowledge of Metabolism.[2] (*Nathan Lewis Hatfield Lecture XXII.*)

March 1. Castle, W. B. The Diagnosis and Treatment of Anemia.[3] (*Mary Scott Newbold Lecture XLII.*)

April 5. Beck, Claude S. The Surgical Approach to Diseases of the Heart.[4] (*Mary Scott Newbold Lecture XLIII.*)

May 3. Kerr, William J. A New Approach to the Etiology and Treatment of Angina Pectoris.[5] (*Mary Scott Newbold Lecture XLIV.*)

October 4. Blalock, Alfred. Shock. (*Mary Scott Newbold Lecture XLV.*)

November 1. Dyer, R. E. The Rickettsioses of North America.[6] (*James M. Anders Lecture XIV.*)

December 6. Karsner, Howard T. Certain Ovarian Tumors Associated with Sexual Endocrine Dysfunction.[7] (*Thomas Dent Mütter Lecture LII.*)

[1] Printed in the *Transactions & Studies*, 4th ser., vol. 7, no. 1, pp. 1–20, April, 1939.

[2] Printed in the *Transactions & Studies*, 4th ser., vol. 7, no. 1, pp. 21–46, April, 1939.

[3] Printed in the *Transactions & Studies*, 4th ser., vol. 7, no. 2, pp. 129–161, June, 1939.

[4] Printed in the *Transactions & Studies*, 4th ser., vol. 7, no. 3, pp. 211–231, December, 1939.

[5] Printed in the *Transactions & Studies*, 4th ser., vol. 7, no. 2, pp. 162–170, June, 1939.

[6] Printed in the *Transactions & Studies*, 4th ser., vol. 7, no. 3, pp. 232–259, December, 1939.

[7] Printed in the *Transactions & Studies*, 4th ser., vol. 7, no. 4, February, 1940.

Lectures for the General Public

January 20. Muller, George P. Surgical Trends and Medical Progress.

April 14. Bond, Earl D. The Modern Interpretation of Mental Disorders.

November 17. Pepper, O. H. Perry. Medical Problems of Advancing Age.

The Sections[8]

SECTION ON GENERAL MEDICINE[9]

Regular Meeting, November 27, 1939

Observations on a Case of Orthostatic Hypotension. Louis B. Laplace, M.D. (*Abstract below.*)

The Nature and Pathology of Irradiation Sickness. Virgil H. Moon, M.D., Karl Kornblum, M.D., and David R. Morgan, M.D. (*Abstract below.*)

Vitamin Deficiency with Particular Reference to Certain Disease States. Michael G. Wohl, M.D., and Joseph T. Freeman[10], M.D. (*Abstract below.*)

Haverhillia Multiformis Septicemia; Its Relationship to Haverhill and Rat-Bite Fevers. William A. Jeffers[10], M.D., F. F. Allbritten[10], M.D., and R. F. Sheely[10], M.D. (*Abstract below.*)

Abstracts

Observations on a Case of Orthostatic Hypotension. Louis B. Laplace, M.D.

Orthostatic hypotension is a syndrome characterized by a pronounced fall of arterial blood pressure when an upright posture is assumed. Convincing evidence indicates that it is caused by a defect of the reflex vasoconstrictor mechanism which adjusts the circulation to hydrostatic changes. Because the nature of the defect is seldom apparent and probably varies in different cases, further study of the subject is desirable.

A case is reported in which the syndrome of orthostatic hypotension was a transient and recurrent phenomenon and was associated with hypertension. The fall of blood pressure could be counteracted by the inhalation of carbon dioxide, by the

[8] For the transactions of earlier (1939) meetings, see numbers 1–3 of this volume of the *Transactions & Studies*.

[9] This Section held 8 meetings during the year, and had an average attendance of 80.

[10] *By invitation.*

production of circulatory stasis in active muscles and by other related stimuli. The studies described suggest the possibility that in this case a defect of the sympathetic receptor mechanism, rather than a tabetic lesion of the nerve tract, was the cause of the hypotensive syndrome.

The Nature and Pathology of Irradiation Sickness. Virgil H. Moon, M.D., Karl Kornblum, M.D., and David R. Morgan, M.D.

Clinical reports indicate that the clinical features and mode of death in irradiation sickness are those of shock. Experiments on dogs confirm this interpretation.

Dogs were subjected to massive Roentgen irradiation over the abdomen. After an interval of 60 to 72 hours, they developed severe manifestations of shock accompanied by hemoconcentration ranging from 15 to 50 per cent. The visceral findings post mortem were identically the same as after shock from other causes.

Our results confirm those of Whipple et al.: Deep irradiation causes delayed necrosis of the intestinal mucosa, followed by circulatory failure resulting from absorption of products from the disintegrating mucosa.

These experiments have a significant bearing on the mechanism of shock. Some writers assign this to local hemorrhage and loss of fluid, or to sympatho-adrenal hyperactivity, and disregard absorption of products from damaged tissues as a factor. Injury to the intestinal mucosa by irradiation eliminates pain, emotional reactions, sympatho-adrenal hyperactivity, hemorrhage and anesthesia as factors. In the experiments described, it appears that the disturbance of circulation resulted solely from absorption independent of other factors.

Vitamin Deficiency with Particular Reference to Certain Disease States. Michael G. Wohl, M.D., and Joseph T. Freeman, M.D.

From a review of clinical and laboratory findings of 368 patients (1904–1938) diagnosed as exhibiting vitamin deficiency disease no well-defined clinical pattern of a general avitaminosis

state could be outlined for diagnosis in the early stages of the disease. Less obvious deficiencies occurring in the course of other disease states are more frequent. An investigation by the dark adaptation method for Vitamin A deficiency was therefore instituted with the aid of Dr. J. B. Feldman in studies of liver and thyroid disease.

Liver Disease: 27 cases of liver disease of various forms were studied in conjunction with the usual liver function tests. The bromsulfalein, the cholesterol-ester and the dark adaptation seemed to yield the most information as to the state of the functional capacity of the liver. In the case of jaundice in liver disease, the dark adaptation was pathologic when jaundice was the result of severe liver damage; the dark adaptation was likewise abnormal where severe liver damage occurred without jaundice. Where jaundice occurred without marked liver damage the dark adaptation curve approximated the normal. The usefulness of dark adaptation as an additional aid in assaying liver function may therefore be entertained.

Thyroid Disease: 50 patients with thyroid disorders were studied. 39 had true hyperthyroidism; 77% of these showed varying degrees of pathology of dark adaptation despite an adequate Vitamin A intake; however, 23% had normal dark adaptation. The prolonged use of iodine or the large intake of food rich in Vitamin A might account for this in this minority.

Additional experimental evidence for the existence of an antagonism between Vitamin A and thyroxin was furnished by Wohl and Soloway, who succeeded in producing specific lesions of avitaminosis A—replacement of various epithelia by squamous epithelium—in albino rats in about one half the usual time by the addition of desiccated thyroid to the Vitamin A free diet.

Experimental and clinical evidence points to a depletion of Vitamin A in hyperthyroidism.

Haverhillia Multiformis Septicemia; Its Relationship to Haverhill and Rat-Bite Fevers.[11] William A. Jeffers, M.D., F. F. Allbritten, M.D., and R. F. Sheely, M.D.

[11] To be published in full in the *Journal of the American Medical Association.*

A clinical differentiation between the types of fever following rat bite has not been clearly established. One of two organisms has usually been recovered: Haverhillia multiformis or Spirillum minus.

A case of Haverhillia multiformis septicemia following rat bite is reported. The clinical features are compared with Haverhill fever and contrasted with sodoku (rat-bite fever due to Spirillum minus).

From a study of this patient and a review of cases of Haverhill fever and fever following rat bite, it is suggested that the Haverhillia multiformis infections are characterized by septicemia, arthritis, and morbiliform and petechial skin eruptions. By contrast, the Spirillum minus infections are comparable with syphilis, manifesting an indolent chancre, regional lymphadenopathy, papular or large macular eruptions, and a regularly recurring fever.

Meeting, December 27, 1939

(Dinner meeting at the University Club: Clark G. Grazier, M.D., U. S. N., guest speaker)

SECTION ON MEDICAL HISTORY[12]

Meeting, November 13, 1939[13]

THE LEGACY OF ROME IN THE HISTORY OF MEDICINE.[14] Arturo Castiglioni,[10] M.D.

Annual Students' Meeting

December 11, 1939

THE HISTORY OF PHARMACOLOGY. Carl F. Schmidt, M.D.
THE HISTORY OF CHEMOTHERAPY. John F. Kolmer, M.D.
MODERN TRENDS IN PHARMACOTHERAPY. Hans Molitor,[10] M.D.

[12] This Section held 7 meetings during the year, and had an average attendance of 50.

[13] Joint meeting with The Friends of the Library.

[14] Printed in the *Transactions & Studies*, 4th ser., vol. 7, no. 3, pp. 264–277, December, 1939.

SECTION ON OPHTHALMOLOGY[15]

The Second Annual de Schweinitz Lecture, November 16, 1939

Second Review of the Published Records of Severe Uveitis with Associated Alopecia, Poliosis, Vitiligo and Deafness. Walter R. Parker,[10] M.D.

Regular Meeting, December 21, 1939

Transcranial Extirpation of a Fibrohemangioma of the Orbit: Report of a Case. Benjamin Souders,[10] M.D.

The Extra-ocular Muscles in Myasthenia Gravis and Hyperthyroidism. Melvin W. Thorner,[10] M.D.

A Clinical Evaluation of Dark Adaptation Tests. Francis H. Adler, M.D., and Robb McDonald,[10] M.D.

The Clinician's Experience with Sulfanilimide. Burton Chance, M.D.

SECTION ON OTOLARYNGOLOGY[16]

Regular Meeting, November 15, 1939

Audible Tinnitus: Report and Demonstration of Two Patients. Joseph C. Donnelly, M.D.

A Case of Pseudo-ménière's Syndrome with Relief of Symptoms. Walter Hughson, M.D.

A Case of Epidural Abscess and Perforation of Dura during Mastoidectomy. William Hewson, M.D.

Amyloid Disease of the Larynx Diagnosed by Biopsy. Chevalier L. Jackson, M.D.

Regular Meeting, December 20, 1939

Consideration of Methods Preferred in Cleft Lip and Cleft Palate Repair. Warren B. Davis, M.D.

Fractures of Maxilla and Mandible. Robert H. Ivy, M.D.

Plastic Surgery of the Nose. Samuel Cohen,[10] M.D.

Prostheses. Oscar V. Batson, M.D.

[15] This Section held 8 meetings during the year, and had an average attendance of 63. The transactions of this Section are abstracted in the *American Journal of Ophthalmology* and the *Archives of Ophthalmology*.

[16] This Section held 7 meetings during the year and had an average attendance of 91. The transactions of this Section are abstracted in the *Archives of Otolaryngology*.

SECTION ON PUBLIC HEALTH, PREVENTIVE AND INDUSTRIAL MEDICINE[17]

Meeting, December 4, 1939

Symposium on Air-borne Infections[18]

AIR AS A VEHICLE OF CONTAGION. W. F. Wells.[10]

THE EPIDEMIOLOGY OF AIR-BORNE INFECTIONS. Mildred W. Wells,[10] M.D.

THE DEVELOPMENT OF MEASURES FOR THE CONTROL OF AIR-BORNE INFECTIONS. Joseph Stokes, Jr., M.D., and Theodore S. Wilder, M.D.

[17] This Section held 4 meetings during the year, and had an average attendance of 66.

[18] The communication from Professor and Dr. Wells, Drs. Stokes and Wilder printed in this number of the *Transactions & Studies* is a synthesis of their respective presentations at this meeting.

The Medico-Mnemonic Treatise (1491) of Johannes Michael Albertus Carrariensis*

By W. B. McDaniel, 2d

Librarian of The College of Physicians of Philadelphia

I

The Antiquity of the Mnemonic Tradition

THOUGH Cicero and Pliny tell us that the celebrated Greek lyric poet Simonides (556–467 B.C.), of Ceos, invented the "art" of memory,[1] it must not be supposed that the Greeks had not, long before his time, recognized the prime importance of the faculty of memory in the preservation and transmission of their traditions and culture. It was not by accident, certainly, that the Homeric narratives passed from one generation to another in the form of metrical verse; nor was it accidental that the Greeks illustrated their characteristically exquisite perception by appointing as mother of the nine muses—Mnemosyne, the personification of memory.

As Simonides came to be the "father" of mnemotechnical systems, so Plato and Aristotle served in later times as the fountain-heads for quasi-scientific inquiries into the nature of memory. These two lines of interest in the subject—the practical and the theoretical—inevitably became more or less intertwined in the studies of later *savants* such as Cicero, Quintilian,

* Based on papers read before the Osler Club of Saranac Lake (1936), the American Association of the History of Medicine (1937), the Philobiblon Club of Philadelphia (1938).

[1] At a dinner attended by Simonides, so the ancient story goes, the walls fell in, crushing to death all the guests but Simonides, and disfiguring the bodies beyond recognition. At this juncture, when it seemed as if personal rites of burial were to be denied the victims, Simonides identified the bodies from his memory of where each guest had been reclining at the time of the catastrophe. This became the traditional origin of the topical, or locality, system of memorizing, which enslaved the minds of the mnemonically inclined for many centuries.

and Seneca. The problems they discovered were handed on to the Church Fathers (Ss. Augustine, Thomas Aquinas), who endowed them with a psychological complexion. In the later Middle Ages, the most often-quoted contemporary authorities on the subject were the metaphysical philosophers and scientists Roger Bacon, Arnold of Villanova, and Raymond Lull. The level to which some of the inquiries had sunk by that time, however, can be estimated by the claim that Lull's system would enable anyone to dispute for an entire day upon any subject without having any knowledge of it whatsoever!

Archigenes and Galen

We know, then, that the subject of memory early became a happy hunting-ground for the great speculative minds of antiquity. We may properly be curious as to the beginnings of an empiric interest in it on the part of practicing physicians.

Archigenes, of Apamea, a fashionable practitioner and medical writer at Rome in the time of Trajan (98–115), was the earliest physician to write on the memory from what we may perhaps call a clinical point of view, so far as I have been able to discover. With his characteristic vivacity, Galen tells us[2] that once, being under the necessity, while still a young man, of finding some means of restoring a patient's memory, and never having seen his masters treat such a case, he sought for a method of treatment in the writings of the ancients, but unsuccessfully. Then, learning that Archigenes (an eclectic pneumatist) had written a book on the subject, he ran to all the libraries and book-stores in search of it, and finally to all the physicians of his acquaintance who were students of Archigenes' writings. Finding a copy at last, he discovered to his amazement that Archigenes, while clinging to the doctrine of his school that the seat of the intellectual faculties was in the heart, nevertheless directed his treatment for loss of memory entirely to the head. Furthermore, he recommended warming and drying remedies without having demonstrated that the loss of memory results from cold and moisture.

[2] *De locis affectis*, Bk 3, ch. 5 (Kühn's ed., vol. 8, pp. 147–160; Daremberg's transl., *Oeuvres anatomiques, physiologiques et médicales*, vol. 2, pp. 548–554).

Archigenes' treatment, as reported by Galen, consisted, first, of bleeding, irrigations, fomentations over the entire body, shaving of the head, and cupping. Then came an application of mustard to the whole of the head. When the mustard had been removed, nitre was sprinkled on the head, and after that the head was bathed with hot water. "You will find no more violent remedy than this in the whole of medicine," Galen observes.

Archigenes counseled, also, the use of apophlegmatics composed of mustard, cress, Cnidian berries, stave-wort, and prescribed sternutatories and medicinal potions composed of violently warming and drying medicaments.

Inasmuch as Galen heaps abundant ridicule on the inconsistent reasoning and violent mode of treatment employed by his predecessor, it would be gratifying, if surprising, to find his own position more tenable. At this point he does little more in a constructive way than compare the loss of memory (which has its seat in the brain) with such affections as melancholia, phrenitis, mania, and epilepsy, in that none of them gives any sign of the place affected—that is, no preternatural tumor, pain, or excretion being manifest. In a subsequent chapter,[3] however, his views on the subject become a little more positive and explicit.

The patient's sleep, for instance, is the first thing to be observed: is it very deep, or moderate, or lacking entirely? From this one will discover which is the dominant dyscrasia. One then must observe whether the nose and mouth are carrying matter down from the head, or whether these parts be dry. In this manner one is able to conjecture the diathesis. The quality and quantity of the excretion, together with one's observation of the causes, indicate the diathesis of the head, whether it be hot or cold. Thus, in the case of loss of memory, or grave injury to it, the dyscrasia is always cold, and it is proper to warm it, but not necessarily either to dry or moisten it. If, however, moisture is joined to the cold, then one should dry it; if dryness be joined, then one must moisten it; but should the dyscrasia be midway between them, it should be kept in that state. I do not find that

[3] *Op. cit.*, Bk 3, Ch. 7.

Galen anywhere recommends specific warming, drying or moistening measures for the dyscrasia symptomatic of loss of memory.

The Later Middle Ages

This, then, briefly summarizes what is possibly the earliest medical writing on the subject of memory by professional physicians. That the Arabic writers who later dominated medical thought and practice in the West consistently wrote on the subject is sufficiently well indicated by the references in the text that concerns us here. Their treatises, or passages, on the memory, as well as those of such celebrated Western physicians as Arnold of Villanova, will be found in the medieval collections of their works.

Why, in the cradle-days of the art of printing with movable type, should there have issued from the presses a relatively large group of mnemotechnical monographs? And why, when the printing of contemporary works was still perhaps the exception rather than the rule, should these monographs, without exception, have been, at least nominally, contemporary works? An obvious, if inadequate, answer to both questions would be that these were the early days of the Renaissance, when interest in intellectual and biological questions was being re-awakened generally; certainly, there can be little wonder that men in any age become curious concerning the nature of a faculty at once so recondite, so malleable, and so influential in directing the course of our lives.

Though the mnemonic literature of the Middle Ages has been by no means ignored by Renaissance and modern scholars,[4] no attempt seems to have been made hitherto to set forth any claims it may have to the attention of students of medical history. Three of the group of contemporary mnemonic monographs

[4] See, for instance, Helga Hajdu, *Das mnemotechnische Schrifttum des Mittelalters*, Wien, Franz Leo, 1936 (Aus dem Jahrbuch des deutschen Institutes des königl. ung. Peter Pázmány Universität, Budapest, 1936). This is especially valuable for its analysis of extant manuscripts; the medical aspect of the treatises is merely alluded to. Professor Dean P. Lockwood, of Haverford College, was kind enough to call my attention to this work, which appeared shortly after I had begun studying the medico-mnemonic incunabula in our library.

printed in the 15th century have, however, a calculated and specific medical content; two of the three were written by noted Italian physicians.[5] The treatise by Johannes Michael Albertus Carrariensis, one of the physicians, is the most comprehensive of the three, the best ordered, though the least known; it serves very well to give us a view of the cultured physician's knowledge of the subject in the closing years of the fifteenth century.[6]

II

Johannes Michael Albertus Carrariensis: De omnibus ingeniis augendae memoriae. Bologna, Benedictis, 1491.[7]

Johannes Michael Albertus Carrariensis,[8] son of a learned physician, Guido, whom he cites several times, was himself a physician, theologian, historian, philosopher, orator, poet, and one of the most prolific writers of the 15th century; and yet none of his works except this one is known to have been printed.[9] He was born at Bergamo (1438), where he practiced medicine, becoming one of the most sought-after physicians of his time. He died at Berg-

[5] Johannes Michael Albertus Carrariensis and Matheolus Perusinus; the author of the third treatise, Jacobus Publicius, was an equally celebrated Italian humanist, who is credited with having done much to re-animate a taste for the fine arts in Italy during the early days of the Renaissance. The first of the sixteen 15th-century editions of Matheolus' work was published about 1474; three of these editions are in the library of the College. Publicius' treatise was first printed separately about 1475; this library has a Paris printing (about 1495), and another in a volume containing two other treatises by Publicius, printed at Venice, 1485. I have studied the works of Matheolus and Publicius as closely as I have that of Carrara, but limitations of space, and the comprehensiveness of Carrara's treatise, make further reference to them here inadvisable.

[6] The range of Carrara's reading may be indicated by a list of the authorities he cites: Pliny (both elder and younger), Cicero, Afranius, Averroes, Albertus (Magnus?), Aristotle, Isaac Salamonis filius (I. Judaeus), Plato, Terence, Galen, Martianus, Boethius, Seneca, Ptolomaeus, Thomas Aquinas, Gorgias, Quintilian, Remigius, Paul the Apostle, Horace, Cato, Ausonius, Hieronymus (St. Jerome), Augustine, Justinian, Avicenna, Johannes Scotus, Turisanus, Gentilis, Haly Abbas, Conciliator (Petrus de Abano), Rhazes, Mesue, Celsus, Maimonides, Gerardus, Bernardus de Gordonio, Claudianus, Serapion.

[7] The only fifteenth-century edition. Copy in the library of the College.

[8] Hirsch and Hübotter's *Biographisches Lexicon der hervorragender Aerzte*, 2. ed., I, 839.

[9] Another of his treatises, extant in manuscript, is discussed by Lynn Thorndike in his *Science and Thought in the Fifteenth Century*, New York, Columbia University Press, 1929, Chapter XII.

amo October 20, 1490; his one printed treatise did not appear, therefore, until a year or so after his death.

In the first of the two chapters of Carrara's mnemonic treatise the stage is set (*f. aia*) by means of a rehearsal of feats of memory attributed to the great: who, for instance, does not admire Carneades, the Greek, reciting from memory, as though he were reading, the contents of the books in an entire library? Cyrus used to call each of his soldiers by name; Mithridates, ruler of twenty-two tribes, understood and spoke the language of each without the aid of an interpreter: feats paralleled "in our own age" by two Venetians, Doge Francisco Foscari,[10] who could recall at the opportune moment anything he had said or done throughout his reign, the names of the persons involved, and the times at which the events took place; and Senator Dominicus Georgio,[11] who most fruitfully united a tenacious memory to his wisdom.

Since Cicero was pleased to hold that memory contains something of art in it, and is not produced by nature alone, Carrara proposes, first, to treat of artificial memory, in so far as it is represented by the system of places and images, and, after that, of the medical means that may be used to acquire and strengthen it.

Simonides *medicus* (sic) is said, Carrara tells us, to have invented the "locality" system of memory, but Metiodorus to have cultivated it much more diligently. If we follow the opinions of the philosophers, there are four movements to the process of memory: first, is the motion of the spirits which transports the images from the cogitative to the memorative faculty; second (*f. aiia*), is the fixing of the images in the memorative faculty; third, is the bringing back of these images, by the spirits, from the memorative to the cogitative faculty; fourth, is the act by which the cogitative faculty recognizes them, and this last is properly called the act of remembering.

[10] Foscari was the elder of *I due Foscari*, whose tragic domestic drama formed the subject of a tragedy by Byron and a now forgotten opera by Verdi.

[11] Senator Georgio is claimed as one of his numerous illustrious pupils by the redoubtable Petrus Ravennas, whose diverting mnemonic treatise (non-medical) was recommended by Robert Burton to those addicted to melancholy.

Following this preliminary little essay in the theory of the memorative process, we are introduced to twenty precepts designed for those who wish to improve their memory. It is not beside the point to summarize the contents of these as briefly as possible. *1.* As the period of youth is the time when impressions are readily made upon the memory, let parents beware of entrusting their children to any but the best studies; *2.* The effort of the mind expended on the understanding of difficult subjects is useful in the development of the memory; *3.* (*f. aiib*) Complete concentration should be given to what is being read or heard; *4.* Many facts should be reduced to a few, as particulars can be derived from general propositions; *5.* Order must first of all be carefully observed, the arrangement of the *Canon* of Avicenna, with its fen, treatises, chapters, conclusions, being an admirable example; *6.* Employ frequent repetition; *7.* Separate a complicated subject into its parts; *8.* (*f. aiiia*) Boethius advises daily cogitation, and also frequent disputation with men engaged in like studies; *9.* Take Thomas Aquinas' advice not to shun the difficult, but master it before passing on; *10.* Heed Quintilian, quoting Plato, and let not the fact of a work's existence in written form be an excuse for not exercising your memory; *11.* And again, learning from Quintilian,—cultivate a good digestion; *12.* Free the mind from extraneous thoughts as much as possible; *13.* Whenever possible, look at, as well as hear, what is to be remembered; *14.* Reply to a question only after adequate meditation; *15.* (*f. aiiib*) Don't tax the memory with more than it can retain: the memorative faculty differs in each of us; *16.* Certain hours and conditions are marked out by nature as best for study: e.g., the quiet hours before cockcrow; an empty stomach, when the mental faculty is not clouded by vapors; *17.* Check up each day on what has been newly learned; *18.* (*f.* (*a4a*)) Begin the practice of memory-exercises when young: like the sword, memory grows rusty without use; *19.* Relax your mind by change of study and by games; *20.* Do not leave your preceptors prematurely.

Carrara next presents (*f.* (*a4b*)) five precepts, culled from Aristotle, which, if followed, should aid the act of recollection.

These recommend arranging in logical order the facts which one wishes to retain for recollection later; also, the use of comparison, contrast, place, time, and effect to make the given object stand out more vividly in the memory. These coincide, of course, with the development of the subject on the oratorical, or rhetorical, side.

Following this, we arrive (*f.* (*a5a*)) at an exposition of the famous topical system attributed to Simonides. The system comprises, as Cicero[12] tells us, the invention of two series of instruments: a series of places, and a series of figures or images to install in them. Cicero thought a hundred "places" enough to take care of one's needs; but St Thomas Aquinas counseled a greater number. These have been invented with many and varying degrees of skill. Metiodorus selected the twelve signs through which the sun passes, dividing each into three hundred and sixty places. Cicero divided his own home into many places in another ingenious fashion. Carrara's father, Guido, derived his places from a series of animals, so selected that the initial letters of their names followed in the order of the alphabet (asinus, basiliscus, canis, etc.). Each of these animals was divided into five areas, head, forefeet, belly, hindfeet, and tail, thus providing for Guido 115 places in which to store his figures or images.[13]

Coming then (*f.* (*a5b*)) to a discussion of the qualities with which one might endow his images or figures, Carrara recommends, first, a use of persons in attitudes moving the observer to laughter, pity, or admiration; for the last, say, images of girls—an inspiration which he discreetly attributes to Avicenna.[14] The

[12] Actually, the *Rhetorica ad Herennium*, Carrara attributing its authorship to Cicero' according to the custom of the time.

[13] Hajdu, p. 110, would seem to credit Jacobus Publicius with the invention of the animal-alphabet system; but if, as Carrara asserts, his father, Guido, employed it, the latter's use would seem to have preceded Publicius', Guido having died in 1457 or 1459 (Thorndike, p. 197). The truth probably is that so obvious a device must have been known and used in one form or another long before either of them appeared on the scene. The Ratdolt editions of Publicius contain a charming full-page woodcut of twenty-five "animals" against backgrounds of "places", illustrating the use of the system.

[14] Petrus Ravennas (note 11) claims to have used the puella-image with unfailing success, but does not attribute its invention to Avicenna.

remaining precepts are of a rhetorical character, drawing upon the idea of association, much like the Aristotelian precepts for aid in reminiscence outlined above. The chapter closes with a politely sceptical reference to a mnemonic practice of Senator Dominicus Georgio, and with the assertion that if the author's judgment be sound, it behooves him to find some system of memorizing more appropriate to those who, like himself, are unable to reach that orator's height of mnemonic achievement.

The second chapter, dealing with medical aids to the memory, occupies, as does the first, approximately twelve quarto pages printed with small-size type. It constitutes, I believe, the period's most complete printed corpus of contemporary medical writing on the subject. Initiating it (*f. bia*) is a discussion of the physical location of the memorative apparatus. Carrara is forced to the admission that among Avicenna, Aristotle, Galen, and one of Galen's commentators, Trusianus (Torrigiano), there is no agreement on the point. But Avicenna, he says, "and the best of the learned Arabs believed it to be in the posterior ventricle of the cerebrum . . . which is now generally agreed to by the physicians." It is recognized that disease may diminish, take away temporarily, or destroy, the memory. Boethius is cited for the story of the eloquent and persuasive orator who, during a fever, was bereft of all his literary skill; and Pliny, for the statement that no other part of man is so fragile and susceptible to injury. Avicenna, Galen tells us, recalled that when a plague arising from cadavers in Aethiopia spread to Greece, those who recovered from the plague had completely lost their memory. But, argues Carrara, if memory can be diminished and lost through disease, so can it be safeguarded and increased with medical aid. He recognizes that the memory may be not only diminished or lost entirely, but so corrupted that it brings back a wrong image in place of the proper one; but as this is a form of melancholy, and is compounded of heat and dryness, he proposes to follow Trusianus in confining himself to the diminished and lost memory only.

Cold and moisture (*f. bib*) are the two causes principally responsible for obstruction of the memory, though Avicenna and Galen attribute the greater influence to the former. Carrara's conclusion is that, whereas cold, "whose daughter is forgetfulness," impedes the motion of the spirits that is necessary to bring something to remembrance, moisture hinders retention. Galen's concept of dyscrasia as resulting from a lack of balance among the four elemental qualities—heat, cold, moisture, dryness—is referred to and illustrated. If dryness dominates, for instance, there is wakefulness, giddiness, and a lack of the superfluities expelled by the nose, the palate, and the eyes; but there will be, on the other hand, much wax in the ears, which has significance for the memory. The present registers itself with difficulty in the memory, though what is already inscribed there is not easily removed. We see this in the aged, who remember beautifully what they did in their youth, but do not retain the memory of what they did within the past year. Dominant moisture, on the other hand, though it permits an impression to be made very easily, just as easily allows it to be lost. Cold makes the mind sluggish and retards recollection. Heat speeds up the motions [of the spirits] and recollection, and the head is hot to the touch. These dyscrasias also can be merely qualities, involving no great amount of matter, or they can be joined to many humors of corresponding qualities. It should not be overlooked that these causes differ sometimes in their location (*f. biib*); for the injuring cause is in the posterior substance of the brain, where memory is located, according to Avicenna; or it is in the *sensus* that is contained in the belly; or it is in a vessel at the surface of the posterior ventricle—for thus does Gentilis interpret the words of Avicenna; although it can even be understood as being in the panniculi, in the commissures of the substance of brain that contain the spirit, or in a vessel in the cranium. For, although Galen says that the affection which carries off the memory cannot be in the cranium, Gentilis says that, if it be severe enough, it can diminish the memory, if not destroy it. Indeed, matter and anything injurious in the temples can be communicated to, and harm, the memory, for that part of the

head can hold a great deal of matter, the muscle is sensitive, and the cranium thereabout is thin, as Haly Abbas intimates in his chapter on the causes of forgetfulness. So also, many other injurious things in other parts of the body can be communicated to, and injure, the memory. Furthermore, matters themselves either form an abscess, as in lethargy, or they do not.

As for prognosis, forgetfulness borne from birth is not easily overcome. If the body be sound except for an abnormal forgetfulness, unless aid be given it destructive diseases are to be feared: lethargy, epilepsy, apoplexy, and others of the sort; for they can be produced by a multiplication of phlegmatic matter in the brain, according to Avicenna and Rhazes. Diseases caused by cold and moisture—common among the nobles (or clergy, *dominis*) and scholars—are more easily checked than those caused by heat and dryness, because it is less difficult to heat and to dry than to do the opposites, especially in the brain, which is a principal member and both cold and moist.

Having come at length to the subject of treatment, Carrara says, we shall begin as follows: If the cause involves the kind of matter that produces an abscess, the treatment accorded an abscess will be given; if the matter is non-abscess-forming, let it disperse before any remedies are applied; because, unless the matter has been expelled, these often are able to do harm, but never do any good.

Where the cause is cold and moisture, therapy has three modes of approach (*f. biiia*): by purging, diet, and lotions and ointments.

After the body as a whole has been purged, especial attention must be given to a clearing-out of the head: and this is done in six ways: first, by means of pills in a preparation such as Galen's hiera, described by Mesue, strengthened with castoreum and colocynth; the pills will be more potent, if the hiera magna is administered with nutmeg or theodoricon. Carrara's own prescription demands the following ingredients: male frankincense, choice myrrh, ginger, powder made from the head of the hoopoe, acorus, hiera major, castoreum and colocynth. These are mixed with turpentine into a paste; a few of the pills, but large ones, are to be taken after a light meal as one prepares to lie down. The

second method is to masticate ginger in the morning, so that much saliva may be expelled. Useful, too, in all conditions are acorus, nutmeg, pepper, and cubeb with mastic; for the remedies to be chosen should both relate to the specific purpose and have a natural strengthening quality. The third method is by inhaling the following preparation: juice of marjoram, juice of acorus, nutmeg, musk-seed. This is warmed and inhaled in the morning, before eating, while one holds the mouth full of cold water which is afterwards expelled. The nose is blown frequently, also, and we shall expectorate often; for in our times one must expect catarrh to be produced even in him who obeys the canons; therefore, it should be expectorated rather than swallowed, so that it may not go into the stomach or chest. The fourth (*f. biiii b*) is a gargle, to get rid of phlegm and strengthen the head. The recipe calls for acorus, seed of marjoram, pennyroyal, boiled and then strained; then add an oxymel, squiliticus (onion root), seed of honey of the rose and mix. This should be gargled lukewarm in the morning. The fifth is friction, first of the body as a whole, then of the head, for this strengthens the head, according to Cornelius Celsus. But the friction should be commenced at the tibia; afterwards the upper parts should be rubbed little by little, always in such a manner that the matter is directed downward, though this should not be done in the case of a full and cacochymous body. Combing of the head is allied to this method, as Celsus and Aristotle tell us. The sixth method employs a clyster, but not a severe one, for the removal of strong matter, for this evacuates [matter] from the lower parts, separates it from the upper parts, as Avicenna says.

The second method of treatment is by regulation of diet. Galen is quoted as saying: "This common error is committed by the physicians—they attend to the evacuation of bad matter from the bodies of their patients, but they neglect to provide against its recurrence." "We, therefore," says Carrara, "shall not neglect this point." The twelve rules which he gives adhere closely to the medieval conventions in such matters. To be avoided are over-eating, the vaporous vegetables and fruits, thin broth (as containing too much moisture), all kinds of onion and

garlic (which penetrate where they should not), wine of too high a vinosity (too vaporous), all foods which remain long in the stomach, such as cheese, excessive fats, pastes, and nuts.

Under the same heading come, also, rules (*f.* (*b4a*)) on the subjects of air, sleep, exercise, coitus, and mental health, quite as if this were one of the many plague tracts of the period. Carrara advises us that the best air is clear and dry and not windy; that, to obtain the most healthful conditions, the windows of our rooms should be kept open. Sleep should never be indulged in at midday, nor earlier than two hours after eating. Exercise should be taken as strenuously as the individual constitution permits, before and not after eating. Coitus should be infrequent and then only in response to nature's prompting. Furthermore, enough time should have elapsed after eating for digestion to have taken place and the superfluities voided. Mental health should be guarded by worrying as little as possible and by keeping our minds occupied in scientific study and contemplation.

The third method employs various lotions and ointments, the preparation and use of which are set forth with some detail. First (*f.* (*b4b*)), is a lotion for external application to the head, to be used not oftener than once in eight days, and then in the morning before breakfast. Another, a vesicatory, if placed behind the ears, will expel a great deal of the moisture. For internal use, there are preparations employing the conventional herbs, stichados (French lavender), marjoram, gariofilum (a spice), zinziber (ginger), myrobalan, sisymbrium, etc. (*f* (*b5a*)). The turtle dove, it is claimed, is remarkably effective, though less so than the head of the hoopoe. We have a recipe for an ointment to be applied to the temples and the back part of the head thrice yearly, in spring, fall, and winter; this will include, in addition to the herbs, specified weights of bird's tongue, of the testicles of a castrated two-year-old, of bear's fat and the marrow of its right leg, or at least of the dried bone of that leg—all this to be mixed in a frying-pan. The author's father, Guido, is responsible for another recipe, which includes the Philosopher's Oil described by Mesue. Carrara has learned that the gall of a leopard is admirably effective, but has been unable to obtain any

to experiment with. Rhazes, Mesue, and Avicenna agree in recommending for a fading memory (and also for white hair) an anacardic compound (*f.* (*b5b*)), though their recipes differ in particulars. "But," says Carrara, "I will give you a safer and more effective recipe than any of these." The recipe contains a full half-century of ingredients and is accompanied by directions for compounding. One spoonful of it may be taken once a week, on an empty stomach; but should it merely be spread over the temples and the seat of memory, it still will work wonders. Most solemn warning is given, however, that the drying up of the cerebrum be not carried to the point of inducing dyscrasia.

The virtues of plain water receive due praise (*f.* (*b6a*)), especially the beneficent effect which water has on the memory. Having a remarkably strengthening effect on the whole body, it prolongs life, gives good color, drives away diseases arising from cold, dissolves pustules, heals all diseases caused by putridity of the humors — especially, the quartan fever. It aids those suffering from paralysis, spasm, and kidney diseases. By copious use of it one individual has lived 150 years in the best of health. But it is to be used discreetly, Carrara warns, by the choleric and excitable, and in summer and in warm climes, generally.

The author concludes his treatise (*f.* (*b6b*)) with a note on Avicenna's recommendation of diamber, with a further recipe of his own, and, finally, with the confession that, though all these recipes are taken from the wise physicians of the past, they are hard to come by and thus will serve the readers he has had in mind.

III

"Art is long, and time is fleeting." There are periods in the history of science, however, when rather the reverse seems to have been true. One reads of the ideas entertained by Archigenes and Galen on the subject of memory, and then one turns to those set forth by another physician nearly fifteen hundred years later: the time is long, but the art may be thought to have remained singularly static.

Fortunately, we are under no illusions regarding the slow

development of medical concepts during the Middle Ages; no one expects to find in the medical literature of the end of that period other than what has generally been found, namely, a synthesis of the slow-moving book-learning of the past, depending for its value chiefly on the critical talents of the individual synthesizer. In that spirit, it is proper now to seek to discover with what critical taste Carrara discharged his self-imposed task.

In the first place, I think Carrara's work rather remarkable for its architectonic quality. Opening with an account of notable feats of memory attributed to the great—a passage designed to arrest the attention of the reader, the author states thereafter in a forthright fashion his intention of treating the subject from two viewpoints, the mnemotechnical and the medical. The first part outlines the memorative process, proceeds through a long series of numbered general precepts designed to strengthen the memory through mental discipline, all clearly illustrated by examples, to an exposition of the best-known mnemotechnical systems. With equal logic, the second part attempts, first, to locate the seat of memory and to consider memory's susceptibility to injury; proceeds to elucidate the chief causes of injury and, finally, sets forth the appropriate medical measures to be taken. Carrara's sense of order might well have been emulated by some of his more celebrated contemporaries.

It would be difficult, even today, to take more than occasional exception to the precepts that comprise the larger part of Carrara's first chapter. He has, on the whole, culled wisely, and there are few of us, I venture to suggest, who might not remember the lost chord a little more easily, if we followed his precepts. It would be easy, on the other hand, calling to mind the author's credulity and his reliance upon some of the less palatable practices of medieval medicine, not to appreciate that the medical chapter, too, is a well-ordered statement of the contemporary medical principles and practices applicable to his subject. It is questionable whether Carrara had available to him more enlightened sources than those from which he drew.

Finally, Carrara's treatise seems to me interesting for the evident attempt to construct a monograph on the subject some-

what in the modern manner; and for its bringing together, thus, the mental and the physical approaches to the subject.[15] It is clear that Carrara, like most of his contemporaries in the early days of the Renaissance, was forced to stress the adoption of a general regimen of health of more or less proved value, since medical inquiry otherwise remained largely on the speculative plane, however dogmatic and self-assured it may seem, in retrospect, to have been. And yet his monograph, because of its curiously rounded point of view toward the subject, faulty though it be in almost every fundamental scientific detail, unconsciously suggests a valid psychosomatic approach to the subject of memory. But it would be absurd to attempt to force undue significance upon a little work that is essentially characteristic of its time. To those of us who may not have had occasion hitherto to learn what the medieval medical thought about the memory was, this treatise, which is an epitome of that thought, serves as able instructor—and that in itself may be regarded as a sufficiently useful function. If there is not a pearl in every oyster, some of us, at least, are not insensitive to the charms of the oyster itself.

[15] Matheolus Perusinus, in his treatise, claims to be the first to have done this, and may very well have been; but his treatise is not comparable, in scope or in scholarship, to that of Carrara.

President's Address*

By George P. Muller, M.D.

The ordinances and by-laws of the College require the president in an annual address to present to the Fellows the affairs of the College.

The total Fellowship of the College on January 5th, 1940, was 686, composed as follows:

Resident Fellows	630
Non-resident Fellows	46
Honorary Fellows (Foreign)	5
Honorary Fellows (American)	5
Special College Privilege	20

During the year there were elected 25 new Resident Fellows. There were two resignations during 1939, and three Fellows were transferred to Non-resident Membership.

We lost 22 Fellows through death, seventeen Active, three Non-resident and two Honorary Fellows. At the request of the Censors memoirs have been, or will be, presented of Doctors Henry K. Pancoast, Floyd E. Keene, Frederick J. Kalteyer, Alfred Stengel, George M. Boyd, Charles P. Grayson, David R. Bowen and Thomas R. Neilson. These will appear in the *Transactions & Studies*. In addition, the Censors have asked that mention be made of the following:

Albert C. Buckley, a graduate of the Medico-Chirurgical College in 1897. He was a distinguished psychiatrist and alienist and medical superintendent of the Friends Hospital since 1918. He was an associate professor in psychiatry at the Graduate School of Medicine of the University of Pennsylvania. He was a member of several special societies and at one time president of the Philadelphia Psychiatric Society. He was the author of "The Basis of Psychiatry" and made other contributions. Dr.

* Read January 8th, 1940.

Buckley was elected to Fellowship in 1916. He died August 17th, 1939 at the age of sixty-six.

Louis D. Englerth graduated from the Jefferson Medical College in 1914. He was widely known as a surgeon, especially in northeast Philadelphia. He was surgeon to the Frankford, St. Joseph's and Philadelphia General Hospitals and demonstrator of surgery at Jefferson Medical College. He was a member of many societies and of the Royal College of Surgeons of Edinburgh. He was elected a Fellow in 1934. He died August 16th, 1939, at the age of fifty.

Ellis E. W. Given graduated from the Medical School of the University of Pennsylvania in 1897 and was on the staff of the Episcopal, Pennsylvania and Jewish Hospitals. He was decorated personally by General Pershing for his services in the war. Elected a Fellow in 1905, he died May 11th, 1939, at the age of sixty-six.

Robert N. Downs graduated from the Medical School of the University of Pennsylvania in 1895. He was chief of the Obstetrical Department at the Germantown Hospital. Elected a Fellow in 1902, he died February 9th, 1939 at the age of sixty-five.

Daniel J. Milton Miller graduated from the Medical School of the University of Pennsylvania in 1878. He specialized in pediatrics and was the author of many papers covering diseases of children. He was a pediatrician to the Episcopal Hospital, but in 1907 removed to Atlantic City where he continued in active practice until 1933, when he retired. He was elected a Fellow in 1894 and died July 6th, 1939, at the age of eighty-three.

Charles N. Davis graduated from the Medical School of the University of Pennsylvania in 1889. He was a well known dermatologist in Philadelphia and at one time dermatologist to the Pennsylvania Hospital; he was also consultant dermatologist to St. Agnes' Hospital and assistant physician to the Department of Skin Diseases at the Howard Hospital. He was elected a Fellow in 1896 and died October 21st, 1939, at the age of seventy-seven.

John McCrea Dickson graduated from the Medical School of the University of Pennsylvania in 1912. For many years he

was chief of the Annie M. Warner Memorial Hospital at Gettysburg, Pa. He was elected a non-Resident Fellow in 1936 and died September 15th, 1939, at the age of fifty.

Edward H. Goodman graduated from the Medical School of the University of Pennsylvania in 1902. He was very active for a time at his Alma Mater and served on the staffs of the Philadelphia General, the Presbyterian Hospital and other institutions. He wrote a book on blood pressure. Later he retired to Dorset, Vermont, and died in March, 1939, at the age of fifty-nine. He was elected a Fellow of the College in 1908 and transferred to non-Resident Fellowship after he had moved to Vermont.

James J. Quiney was elected to non-Resident Fellowship in 1936. He was Roentgenologist to the Easton Hospital and to the Warren Hospital, Phillipsburg, N. J. He died on March 31st, 1937, at the age of fifty-six years.

William J. Mayo died July 28th, 1939. He was elected an Honorary Fellow of the College in 1906. So many memoirs of him have appeared that any extended mention of his life and achievements would be superfluous here, even if such were obligatory. He was "a great physician, a superb surgeon, a magnificent leader, a beloved man."

Walter Drew McCaw, Brigadier General, U. S. Army, was elected an Honorary Fellow of the College in 1912. He entered the Army in 1884 and was quite active in his army career. He was assistant surgeon general at the time of his retirement in 1927. He was the recipient of many honors here and abroad. He died July 7th, 1939, at the age of seventy-six.

Herman B. Allyn graduated from the University of Pennsylvania in 1885. He was in active practice in West Philadelphia for many years. He served on various committees of the College and until his final illness was one of the most faithful attendants at our meetings; in addition, he was always interested in the Philadelphia County Medical Society and was its President in 1920. At the time of his death he was consulting physician to the Woman's Hospital and the Philadelphia General Hospital but for many years had been physician to the latter institution. He

was particularly interested in diet control and the care of the aged. He was elected a Fellow in 1896 and died November 6th, 1939 at the age of seventy-nine years.

Collin Foulkrod graduated from the Jefferson Medical College in 1901. He served his interneship at the Presbyterian Hospital and had been a member of the staff since. He was assistant professor of obstetrics at the Jefferson Medical College and author of many medical treatises. He was a past president of the Philadelphia Obstetrical Society and also a member of the American Board of Obstetrics and Gynecology. Elected a Fellow in 1908, he died November 16th, 1939 at the age of sixty-five years.

Henry M. Fisher graduated from the University of Pennsylvania in 1875. He spent two years studying in Vienna and Paris and then returned to Philadelphia. He served as the head of the Out-patient Department of the Pennsylvania Hospital (1882) and for many years was on the staff of the Episcopal Hospital. He resided at 1020 Pine Street until two years ago, when he moved to Jenkintown. He was elected a Fellow in 1884 and died on April 27th, 1939 at the age of eighty-eight.

As a result of the deaths, resignations and transfers we note that although 25 Fellows were elected during the year the net increase has been only three. We can be proud of the way the membership of the College has held together during these difficult years.

The Council has continued its careful scrutiny of candidates to be submitted to the College and I am pleased to note that last year no candidate approved by the Council has failed of election by the College.

The *finances* of the College necessarily hold a major interest. The Pennsylvania Company estimates the total assets of the College, exclusive of 13th and Locust Streets, to have increased by about $18,000. The principal items in this estimate are a write-off of $100,000 in the value of property and mortgages held, and an appreciation of $130,000 in the book value of the College's portfolio, $63,000 of which represents bequests. There were no further defaults in our portfolio during 1939 but we have bonds,

still paying, whose position is precarious. The yield on our securities is 4.84 per cent and as shifting is done for greater security a reduction in the yield is inevitable. This must be done with great circumspection because if we were to invest our funds completely in securities of the highest grade the low yield would paralyze the activities of the College.

The budget for 1939 allowed a surplus of $200 and this was exceeded by $730, but the budget balanced because of back rent obtained from the tenant at 13th and Locust Streets. The Committee therefore felt it imperative that the budget for 1940 contain a surplus of $500, and that expenditures be rigidly confined to the estimate, but unfortunately last minute contingencies have reduced this surplus to $239. Certain items such as taxes, pensions, insurance, and salaries cannot be cut and we are left with the alternative of pressing down on the library, the hall and some miscellaneous expenditures. The library of course is our greatest asset and while not essentially reduced in the 1940 budget, needs more money. $7600 has been allocated to the library and it will have about $18,400 from the special funds earmarked for the library.

The building is getting older and needs extensive renovating but we can only patch here and there within the margin of safety. A fair item of expense is the publication of the *Transactions & Studies*, but it should be remembered that this is the only link connecting the College with many of its Fellows who neither use the library nor attend the lectures, and with similar institutions elsewhere. Part of the cost of publishing the *Transactions & Studies* is provided for by endowed funds. The Publication Committee has no secretarial help.

Last year I suggested the possibility of grouping all of the funds of the College into a single fund and the employment of a paid investment councillor. For various reasons we never developed the first, and as for the second we found the expense prohibitive at this time.

Special donations have been given for the improvement of the room to the right of the entrance, called the President's room. The present condition is only temporary and further efforts should

be made to solicit funds to furnish this room in keeping with the tone of the College. The opposite room, the clerk's office, also needs refurnishing with modern office equipment.

As a result of a trifling fire developing from the motor controlling the library stack lift the question of insurance on the books has become a matter of importance. The subject is quite complicated owing to the impossibility of estimating the factors that determine the value of books and is discussed in the report of the Hall Committee on file in the office. Presumably we have a fireproof building and our contacts on all sides of the building are good from the standpoint of fire hazard. However, the Hall Committee, after discussions with insurance brokers, recommends that the present insurance policies on the building and its contents be re-studied to determine whether a new basic rate might be applied, resulting possibly in a saving that in turn might be applied to insurance on the books. Immediate measures that will be undertaken are a more extensive watchman's clock system than we have now and equipment to prevent smoke or fire reaching the book stacks through ventilating ducts.

The *library* inventory shows the accessioned items to have been increased by 2421, so that the total number now is 152,454. In addition, there are over 316,000 unaccessioned items, most of which are pamphlets of less than 100 pages. We now have 410 incunabula. About 10,500 visits by non-Fellows and about 2,300 from Fellows show the interest taken in this great library. 8524 volumes were taken out, and nearly 50,000 volumes were consulted in the library.

The use of the study rooms greatly increased over last year, almost trebled in fact, and there was a great increase in the demand for photostats. Many other figures might be given you, but they will be presented in the report by the librarian.

The library had other activities apart from the loan of books. "A memorial exhibit of the published works of Dr. Sigmund Freud was presented a few days after the author's death. Other extensive exhibits were devoted to the subjects of endocrinology, anemia, allergy, and to works illustrating the major advances in the history of surgery. Following our custom, a special exhibit

was prepared for each of the meetings of the Section on Medical History. There can be no doubt, if one may judge from many comments, that these exhibits contribute materially to a better general knowledge of the library's resources and to the development of a historical perspective, in both our readers and ourselves" (*Library Report*).

We are preparing a list of the library's holdings of serial publications for the next edition of the Union List of Serials, and revising the more extensive groups of subject-cards in the catalog so as to indicate at a glance the works published before 1900 and those published after 1899. Through the generosity of Dr. C. W. Burr we have acquired an Argus microfilm reader; some believe that microfilm reproduction bids fair "to become the greatest single aid to scholarly research since the invention of printing with movable type."

I hesitate to "gild the lily" but must once more mention the indefatigable labors of W. B. McDaniel, 2nd, our librarian, who not only acts as the dynamo of the library but also has adorned many meetings by his expert knowledge of library matters. The College must also realize its indebtedness to the expert staff of eight workers who so ably assist the librarian.

The *Transactions & Studies* of the College have been issued quarterly and attain a high standard of literary effort as well as serving to bring to the attention of the Fellows the more important facts regarding the work of the College. The Publication Committee has done a good job.

The *Program Committee*, under the Chairmanship of Dr. Edward Bortz and the Committees in charge of the various Foundation Lectures, submitted a program of eight lectures of the very highest caliber. In 1937 the average attendance was 221 with a high of 325 and a low of 80. In 1938 the average attendance was 326, with a high of 550 and a low of 121. Last year the average attendance was 291 with a high of 425 and a low of 148. The average attendance in 1939 was less than in 1938 but greater than in 1937. The Program Committee should analyze the attendance of the last three years as related to the titles of the papers read. The matter of title is of great im-

portance in the average physician's decision whether or not to attend the lecture. There has been a tendency toward longer lectures and I think this is a mistake. Forty-five minutes, including the time used for lantern slides, is quite enough; after this the audience usually gets very restless.

We have four funds, namely, the Nathan Lewis Hatfield, the Thomas Dent Mütter, the Mary Scott Newbold and the James M. Anders, whose committees have a certain measure of control over lectures. The present policy of the College is to obtain distinguished investigators for most of the lectures and as stipends must be paid the only funds available are in these endowments. It seems to me that the Committee on Scientific Business must be responsible ultimately for the program in order to coördinate subjects and follow the general policy of the College, which may change from time to time, and hence the committees in charge of these funds should confer with the committee of Council in arranging lectures.

The series of Lectures for the General Public attracted an average audience of 227. The subjects were "Surgical Trends and Medical Progress," by George P. Muller, "Medical Problems of Advancing Age," by O. H. Perry Pepper, and "The Modern Interpretation of Mental Disorders," by Earl D. Bond. These lectures serve the important principle that we are an educational institution and represent a public asset. Looking at it from this point of view they are worth the cost of advertising. The College is greatly indebted to the Fellows who gave these lectures without cost to the College.

A good suggestion has been offered by Dr. George M. Laws, namely, that the women's committee now in charge of the garden might be persuaded to assume an active part in furthering interest in the series of public lectures.

A number of the exhibits of the *Mütter Museum* were rearranged during the past year, leading to a better grouping, and thus making the exhibits more available for observation and study. The assemblage of all specimens of tumors was completed during the year.

The important gift has been the Matthew H. Cryer Anatomical

Collection, consisting of a large number of dissections of the face, teeth and jaws, given permanently by Mrs. Cryer.

A bottle containing a specimen of opium was deposited in the Mütter Museum in 1853 by Dr. C. D. Meigs, with the directions that the bottle should not be opened for fifty years. The specimen remained unstudied until 1939, when, at the request of the Mütter Committee and the curator of the Museum, Dr. H. C. Wood and Professor Arthur Osol, of the Philadelphia College of Pharmacy, made an assay of the specimen. Apparently, after 86 years, the assay showed that the quantity of morphine as present in opium, is substantially stable.

In furtherance of this study and with the acquiescence of the Mütter Committee, Dr. Wood and Professor Osol prepared a paper entitled, "Assay of a Sample of Opium nearly Ninety Years Old with Some Remarks on the History of Morphinometric Assay." The paper is properly credited to the Mütter Museum of the College and published in the *American Journal of Pharmacy*, Vol. 3, October, 1939.

If sufficient funds are available to the Museum a complete revamping should be done to improve its educational possibility. As it is now, it tends to become a repository of items of historical interest, although the collection representing bone pathology probably is unsurpassed. The annual lecture on surgical pathology attracts a large and interested audience and this year was given by Dr. Howard T. Karsner of Cleveland on "Certain Ovarian Tumors Associated with Sexual Endocrine Dysfunction."

The *Alvarenga Prize* for 1939 was awarded on July 14th, 1939, to Dr. Harry Goldblatt of Cleveland for his outstanding contribution to the pathogenesis of hypertension.

The *College Collections* have had numerous additions, especially of medals and etchings. Renovation of the College portraits has continued and a catalog of the entire collection gotten well under way. Dr. Joseph McFarland has continued his efficient work as curator of both the Mütter Museum and the College Collections.

Hall Committee. This Committee has charge of the physical equipment of the College building. The condition of the building

has been guarded and improved insofar as circumstances permitted. Two sections of the roof have been repaired, the motor controlling the lift in the book stacks has been replaced, several of the rooms have been painted. Thomson Hall has been improved by changing the direction of the seats, and the stations for the projection machines in Mitchell and Cadwalader Halls were shifted and elevated. Lighting improvements were made. The replacement and addition of signs about the building might be mentioned.

The Committee recommends consideration of the advisability of installing a checking system in the at present completely unguarded coat-room. The reason for this is quite obvious.

At this place mention should be made of the much appreciated activities of the Women's Committee. A very necessary retaining wall was built in the garden, approximately on the dividing line between the garden and the church property to the south. As a result they were enabled to forward the plans for making the garden one unique in this city and appropriate to a medical institution.

The *Committee on Public Health, Preventive Medicine and Public Relations* is most important in that it enables the College to officially contact the public. I believe that the chairman of the Section on Public Health, Preventive and Industrial Medicine should be one of the members of this Committee of the College, and that the Committee should direct the programs of the Section. The influence of the College in public affairs could more easily be attained if this Committee and this Section worked together. An effort should be made to give the Committee funds to aid the programs of the Section. I can envisage the time when the Sections on Medicine, on Medical History and on Public Health are brought closer into the College itself and together with the College lectures and the lectures to the public, will present a planned effort to place the College in greater prominence as a leader of medical thought. The philosophy of leadership includes something more than leadership in that which is termed today medical economics and which wisely is left to the County Medical Society.

This Committee increased their activities during the past year, usually working in combination with the similar Committee from the Philadelphia County Medical Society. A good deal of the work which they undertook came to naught because of the defeat of the plan for introducing a new city charter. The combined committees made another investigation of the Philadelphia State Hospital, formerly called Byberry Hospital, since its transfer to state control. They reported a marked improvement of conditions previously censured, and commended the management of the new director, hoping that he would be supported and defended against unwarranted criticism.

Through releases to the newspapers the public was informed of the existence of a widespread infection of the respiratory tract last spring and advised as to proper measures of prevention. Similar publicity was given in regard to Rocky Mountain spotted fever, which occurred in May and June.

Our Committee and that from the County Medical Society will continue their work during this year, the important problem before them now being that of the city water supply. It is proposed to have a conference with the city engineers and others interested in the subject to discuss ways and means of improving Philadelphia's water supply and prevention of pollution of the Delaware and Schuylkill rivers.

The matter of tenure of office on committees has been discussed informally many times by members of Council but the solution is not easy. In 1900 W. W. Keen in his presidential address proposed that in the case of the Standing Committees the senior members of the committees should be omitted from eligibility for one year. But we do not have a progressing term in the committees and further it would not be wise to change the complexion of the Council too widely. I believe, however, that it would be wise to limit the term of office of the chairman of a Standing Committee to not more than a three year consecutive term, as is provided in the case of the elective councillors.

Sections. The various sections of the College have been active and numerous valuable scientific contributions were presented at the meetings. The average attendance was 80 in

the Medical Section, 63 in the Ophthalmological Section, 91 in the Otolaryngological Section and 50 in the Section on Medical History. The Section on Public Health, Preventive and Industrial Medicine averaged an attendance of 66 and the most important meeting, namely, that on tuberculosis prevention, had the largest attendance (130). It is interesting to note that the meeting devoted to medical economics attracted only 34 persons. I believe that this matter of "medical economics," using the term in the political sense, is lessening in interest and importance to local groups and being pushed into the programs of the State and National organizations. There are many items of public interest which this Section can present in an attractive way and help the College to continue leadership in the local health problems. I believe, as I have said, that the chairman of this Section should be an ex-officio member of the College Committee on Public Health, Preventive Medicine and Public Relations.

In concluding this address I must express the satisfaction and gratitude of the College to the officers and Fellows serving on the Committees for their arduous and time-consuming efforts in the service of the College. No salaries are paid, yet the attendance is remarkable and I know of no other scientific group who work more enthusiastically for the good of their institution.

We are most fortunate in having the guiding hand of W. B. McDaniel, 2nd. He is the spark plug of the College and not only stimulates the library and literary efforts but works untiringly as superintendent of the building. We should also mention the work of Mr. R. G. Muir, the assistant to Mr. McDaniel, who directs the Hall Staff and saves the College considerable money by taking care of many of the jobs in the building. Miss Olga Lang, the clerk of the College, is indispensible to the Secretary and Treasurer and, a host in herself, is ably assisted by Mrs. Nash.

As for myself, the honor of having been president of this ancient and illustrious institution for three years is sufficient reward for the efforts in its behalf.

Report of the Library Committee*

As THE statistical part, the marrow, of our report, retains the characteristic features of its immediate predecessors, showing a reasonable degree of maturation where that is desirable, but offering no particular occasion for special interpretation, it seems possible that some of the Fellows might be interested in a brief glimpse into the workings of the machinery that puts into the reader's hands the book or article in which he is interested. Readers tend, we find, on the one hand to simplify the process, in their own minds, to the mere stamping of "Date Due" and "Date Returned" on their books; on the other, to become unduly bewildered when faced with the discovery that a large library is a rather complex organism governed by natural laws of its own. Let us say, for instance, that a reader is allowed to consult a book or periodical not yet prepared for circulation. He is seen to be holding it up in the air and slashing open its pages, thus straining the binding and leaving the pages with rough or torn, and unequal, edges. If he is reminded gently that the publication is likely to remain longer in good condition if its pages are cut while it is lying flat on the table, his bewilderment is sometimes expressed in some such facetious rejoinder as, "Oh, that's just the librarian in you!"

Perhaps both these points of view, expressed usually in the friendliest and most indulgent of terms, have their origin in what may be called the layman's innocence of knowledge regarding the technique of a profession alien to his intimate experience; and, if so, one knows that there is nothing more likely to induce us to alter an opinion (at least, one not grounded in the emotions) than a little elementary information. The library world has no Hippocratic Oath, binding us to secrecy; and if our terrible, secret practices continue to seem generally mysterious and arbitrary to our patients, and if this results in misunderstanding, then the

* October 16, 1938–October 15, 1939. The annual reports of this library are customarily based on corresponding periods.

only real culprit is our own stupidity in not taking our patients into our confidence, insofar as they are willing to receive it.

What follows, then, is an attempt to give to the Fellows a suggestive outline of the rational (we believe) mechanism against which they occasionally bump their heads, but which, nevertheless, has probably answered their needs quietly and successfully on other occasions.

The Selection of Books and Periodicals

The present rate of production of medical books and periodicals makes a judicious selection for a library with a limited budget an extremely difficult matter. The problems raised by the amoeba-like character of modern medicine was considered in our last report. Here, we confine ourselves to describing the methods of obtaining information as to new publications. Both the library *Booklist* and the monthly College notices carry statements that the recommendations or requests of Fellows will be given first, and prompt, consideration. A box in which slips containing recommendations may be placed is kept in a prominent place in the Reading Room. Recommendations or requests from these sources are, frankly, not many. From an agent in New York come on approval many books of foreign origin; a few publishers in this country send their books on approval, without waiting for a specific request, but in most cases the American publishers rely upon their frequent circulars. Reviews in the leading medical periodicals are combed for suggestions as to worthwhile books that have escaped us, and so are the booklists of other medical libraries.

A sub-committee of the Library Committee, acting in consultation with the librarian, makes the decisions as to purchase. Occasionally, when the committee is unwilling to pass upon a book in a highly specialized field, advice is sought from a member of a much larger, though wholly unofficial, committee. A Library Committee rule authorizes the librarian to purchase without further consultation any work requested by two Fellows of the College, unless for some reason, such as great cost, he feels it desirable to consult the committee before ordering.

Since a number of publishers, authors, and other friends regularly present books to the library, obviously it should not be assumed that all books listed on the *Booklist* were purchased by the library, or that they have the approval of the Library Committee. It might well be borne in mind constantly, as was suggested in our last report, that we have many minds to feed, many aims ourselves to keep in mind.

The Book Is Ordered

When purchase has been decided upon and the order goes forth, a record of the order is kept, containing all essential data about the book. Attached to this card is the circular, card, or slip bearing the initials of the committee-members authorizing the purchase, as well as the names of any readers who have asked for the book; when the book becomes available for use, these readers are the first to be so informed. Another card-file contains similar data about the "rejected" books, while to a third is transferred the order-card as soon as the book has been received and the fact noted on the card. Obviously, it is important that these records be kept accurately, as they furnish quickly a fund of useful information, in addition to preventing more than one order being sent out for a single book.

The assistant in charge of the orders, incidentally, types all outgoing letters that are not of primary concern to either the circulation or periodicals departments, and classifies by subject or (in the case of Fellows) by the alphabetical order of authors' surnames the thousands of reprints and other pamphlets received in a year's time.

The Book Undergoes Ceremonies of Initiation

After the fledgling book has been received and the fact has been noted on the order-card, it enters upon the ceremonies of initiation. First, it cools its heels while an assistant "funds" it; i.e., pores over the balances in 40-odd funds, seeking one that is restricted to the subject with which the book is concerned (fortunately, it is now recognized by most prospective benefactors that restricted bequests often hamper the realization of the philan-

thropic purpose that motivates the bequest), that is not too much engaged in its obligations to periodicals in the same field, and that is otherwise solvent: failing in this quest, the assistant assigns the bill to one of the rarer general funds. The book having been made, thus, at least nominally ours, it is promptly marched off to the cataloguer.

The library's classification system is, as might be expected in a pioneer library, one of the older ones in use by medical libraries. Based in general on that of the Army Medical Library, it is amended from time to time as the succeeding volumes of the Index-catalogue appear. But no classification system in existence could solve all the problems with which a cataloguer is faced; she must get guidance from other tools, such as the *Quarterly Cumulative Index Medicus*, and often, in the end, rely on her own judgment alone. The cataloguer must know the standards adopted by libraries generally and adapt and adjust the particular to the general insofar as that can be done. In order to prevent chaos, libraries have adopted techniques that often, to the uninitiated, seem arbitrary and designed villainously to withhold information, but that, like techniques in other fields, actually preserve order and more quickly dispense information to those who understand the need for them and take the trouble to learn them. The cataloguer seeks as much as possible to preserve the standards that make for order, while, by means of cross reference, she attempts to speak what is to her the language of the layman.

The cataloguer, then, studying the new book in conjunction with the classification systems, must decide what the primary classification is to be, what the subsidiary ones; and, finally, must attempt to approximate the "layman's" approach by a number of less scientific classifications. It is obvious that, in a library as large as ours, she must have at least a superficial knowledge of a half-dozen foreign languages.

When the cataloguer has decided upon the proper classifications of the book and assigned it its chronological number within the primary classification, the assistant in charge of orders prepares the appropriate bookplate, slips it in the book, and dispatches the

book to another department, where it submits to a complete physical examination, called "collation," at the hands of one of the junior assistants. If anything about it — the binding, lettering, pagination, etc. — is imperfect, the librarian is consulted; if he believes the defect serious enough to warrant it, the library puts in a request for another and perfect copy of the book. While the book is being thus collated, the assistant is noting, and putting in slips calling attention to, photographs or other illustrations of a non-technical sort, as well as biographies of various kinds. If the book receives a clean bill of health, the bookplate is pasted in and the book is off to pay a call on the assistant cataloguer.

The cataloguer's assistant writes the cards that the reader consults in the catalogue. In the case of a monograph on a relatively independent subject, a mere half-dozen cards may suffice; if the book is an important one on a more general subject, with sections, handled by separate writers, that are practically monographs in themselves, or if it is copiously illustrated by historical photographs, the number of cards required for the single book may easily run up into the hundreds. There must be a shelf-list card (the shelf-list, kept in the cataloguing room, records the books under their classification numbers, furnishing a useful and necessary means of checking), a card for the *Booklist*, and one to be sent down to Philadelphia's great Union Library Catalogue, at present housed in the building of the Historical Society of Pennsylvania, in addition to the author and subject cards; there may be cards required, also, as we have suggested, for portrait, autograph, bibliography, manuscript, printer, illustrator, sponsoring foundation or committee, and other special index-files incorporated in the Reading Room catalogue. Since the information that goes on each of these cards differs in one or more particulars from that on the others; since that information must be given as accurately as possible if errors arising from this source are not to be perpetuated endlessly, it may readily be seen what responsibility rests on the clearheadedness and sense of accuracy of this assistant, whom the readers know only by her work. It is obvious that she, too, must have varied linguistic accomplish-

ments, if this work is to be done accurately and efficiently. As a check on errors that might creep into the catalogue, each card is read by both the cataloguer and the librarian before it is filed.

But this assistant's duties do not end with the writing of the cards: each book that she handles must also be entered in the accession-book. Twenty-one of these books tell us the dates (in chronological order) on which all the books were made members of the library family, their authors, titles, publishers, years of publication, sources, costs, insofar as all these data were known at the time. When, finally, the accession number, the date of accessioning, the library's stamp, and the "Date Due" slip have been added to the book, it passes through the hands of the cataloguer and the librarian to the shelves reserved for new books. The statistical part of this report indicates that a numerical record is kept of all the chief operations engaged in by this and the other departments.

The Book Is Ready for Circulation

From the reader's point of view, the focal center of the library is, naturally, the circulation desk: here his books are asked for and stamped, and to the assistant in attendance most of his inquiries are addressed; hereabout are the catalogue and the various indexes and works of reference.

The withdrawal of a book involves complexities of which the casual reader is seldom aware. If one calls on the telephone to renew the time on a book that he has out, the assistant must quickly find his slip, either to make the change on it, or to tell him that others (whose names have been written on the slip) are waiting for the book: the readers' slips are therefore arranged in the alphabetical order of their surnames. But if someone asks for a particular book, it would obviously be inefficient to send one of the junior assistants into the stacks, perhaps only to find that the book was not in: therefore, a separate file of slips, arranged under the classification symbols, must be made out and kept beside the reader-slips. These additional slips may number a thousand a month. Each day the assistant must go over all of the reader-slips in order promptly to notify any readers whose books have been retained over the specified time. This assistant,

furthermore, is the telephone switchboard operator, types and stencils the *Booklist*, collects the data for, and types, the monthly (as well as annual) Library and Hall Committee reports; handles all ordinary arrangements for the inter-library loan of books and the use of study rooms, the photostat, and microfilm reader; checks bookdealers' catalogues and the lists of duplicates offered through the exchange bureau of the Medical Library Association; types such outgoing letters as concern the functions of her department. Perhaps the most important of these functions is the answering of innumerable inquiries. Though the library is equipped (through Mrs. Moore, its semi-official assistant) to handle extended research questions, the regular staff can attempt to answer only inquiries of a relatively simple nature. To do even this satisfactorily, the assistant must have a good knowledge of the general sources of information and of the library's own collections, an excellent memory, and, above all, the patience and tact that come from a desire to be of help, even under occasionally trying circumstances.

The Current Periodicals

Of the 1,202 periodicals currently received in the library, 800 are available for consultation by readers on the open shelves in the Current-periodicals Room. They come from all parts of the world, in many languages. Each of the 14,748 separate issues is collated exactly as if it were a book. The fragile nature of these publications, the long journeys that thousands of them undergo, the often erratic methods of editors and publishers result in far more numerous casualties than those that prevail in book-publications: the correspondence entailed in claiming missing or defective copies is, therefore, endless. On special cards record is kept of the receipt of each number, of the source from which the periodical comes, of its cost, if it is purchased; and as current and unbound periodicals are permitted to be taken out only over night, particular care must be taken that a completed volume be bound as soon as possible after receipt of the first number of the succeeding volume. Typewritten lists of the periodicals currently received are kept up-to-date and available for the reader's use, as is a subject-classification in card form.

As this department, too, comes intimately in contact with the reading public, inquiries are numerous and varied. It is essential that the assistant in charge have at least a superficial knowledge of the major foreign languages and a knowledge of the alphabets of some others. It is obviously highly desirable that the assistant, while collating the periodicals, have in mind the special interests of the most frequent users of the periodicals, while the attention of other departments of the library must be promptly called to material that concerns the several activities and special interests of the College and its Fellows. Not least is the obligation to keep a protective eye on the thousands of separate issues exposed not only to abduction, but to a fate hardly less severe, occasional defilement by an inconsiderate reader.

The Work of the Junior Assistants

There are times, but not many, when one or both of the junior assistants are not engaged in fetching books from the stacks or in restacking them. In these moments they are collating books, the newly-bound periodicals, and periodicals irregularly received, operating the photostat, preparing volumes of periodicals for the binder (this requires, of course, the careful making of lists), checking hundreds of books received as gifts (to weed out the duplicates), arranging duplicate books and periodicals in some semblance of order in the basement duplicate room, preparing lists of duplicates to be offered to other medical libraries through the Medical Library Association's exchange bureau.

The End

The reader who, as a neophyte, has followed us through this little tour of inspection might well be forgiven for turning now to the *Hauptmann* and asking: And what, pray, do you do? In addition to writing annual reports, the reply might be, my duty, putting *multum in parvo*, is to attempt to bring into harmonious order, in evolutionary currents, many things—shoes, ships, sealing wax, and cabbages and kings.

The story, as we have told it, is, of course, not complete, and there has been no thought of representing the machine as a streamlined model of superlative efficiency. But if we have been

able to dispel, even in the slightest degree, any idea that the library technique is the librarians' private little joke; if we have been able to suggest at all convincingly that the librarians, far from being drones or eaters of little children, are merely hard-working members of the human family, doing a job that has technical standards, and responsibilities, we shall be grateful. Generally speaking, one supposes, the more we know of the technical methods and the problems of one another's jobs, the easier it becomes to arrive at a just and tenable opinion of the way they are being used and met.

Inventory

	1939	1938	1939	1938
Total number of accessioned items[1]			152,454	150,033
Incunabula	410	409		
Manuscripts	536	524		
Other items[2]	151,508	149,100		
	152,454	150,033		
Total number of unaccessioned items[3]			316,208	309,177
Reports and Transactions	25,530	25,411		
Periodicals "reserve"[4]	4,614	4,594		
More or less complete volumes of other periodicals not regularly received	2,988	3,053		
Theses and dissertations	45,992	41,117		
Pamphlets (less than 100 pages)	237,084	235,002		
	316,208	309,177		
Total number of current periodical publications regularly received			1,202	1,184
Duplicate books			13,100	11,775
Portraits[5]			39,938	35,598

[1] An accessioned item may be any kind of graphic material that is kept within covers, whether these be made commercially or in the library, of paper or of more durable material. The accessioned item might comprise, for instance, part of a book, or one or more books; a part of a periodical volume, or one or more complete periodical volumes; reports, pamphlets, or theses, single or collected; an atlas or photograph album.

[2] Including 46 rare books acquired during the year.

[3] While the accessioned items contain some material in paper covers, it should be noted that most Reports and Transactions, pamphlets, and theses, also paper covered, are not accessioned, but all might be at any time, if any intrinsic reason for so doing should present itself.

[4] More or less complete duplicate volumes of important and much-used periodicals.

[5] Including 105 oil and 548 other, framed portraits in the care of the Committee on College Collections. The count of portraits represents the number of entries on the cards in the portrait catalogue. The entries represent, in turn, both loose portraits and those in books, many of them being merely different reproductions of a single original.

Distribution of This Material

	Accessioned items	*Unaccessioned items*
General Library (including the Lewis Library)	148,240	316,204
On permanent deposit:		
Gross Library	3,798	4
Parry Library of the Obstetrical Society of Philadelphia	217	0
Mütter Museum[6]	199	0
	152,454	316,208

Current Periodicals

Total number of periodicals regularly received in the library: 1,202 titles

	Purchase	*Exchange*	*Gratis*	*Annuals & 'Books'*	*Total*
American (United States)	142	60	160	46	408
Australia and New Zealand	1	3	2	1	7
Belgium	13	7	2	1	23
British Isles	76	19	6	9	110
Canada	1	6	5	2	14
Ceylon and India	2	7	2	1	12
Cuba and Puerto Rico	0	6	4	0	10
France and Colonies	115	16	7	6	144
Germany[7]	154	0	2	28	184
Italy	79	21	6	0	106
Japan, Korea, Manchoukuo	5	14	5	3	27
Mexico and Guatemala	0	4	2	0	6
Netherlands and East Indies	10	1	2	0	13
Russia	3	9	2	0	14
Scandinavia (Denmark, Finland, Norway, Sweden)	12	5	0	2	19
South America	4	19	18	3	44
Spain	0	1	0	1	2
Switzerland	24	1	3	0	28
Miscellaneous[8]	3	20	6	2	31
Totals, 1939	644	219	234	105	1,202
(Annuals & 'Books')	44	29	32	105	
Grand Totals, 1939	688	248	266		1,202
Totals, 1938	662	252	270		1,184

[6] The books of the Mütter Museum are not permitted to be removed from the College building.

[7] Including the former state of Austria.

[8] Fewer than 6 journals each, from: British Africa, China, Czechoslovakia, Egypt, Estonia, Greece, Jugoslavia, Lithuania, Palestine, Philippines, Poland, Portugal, Roumania, Syria.

These figures give the number of only those publications received regularly and currently. One or more numbers of 152 other journals, also, were added to the files during the past year, scattered issues having been received by donation. Still another group of some 20 publications issued not more than once annually and not received during the past 12 months ending October 15, is omitted from the census. Of 43 other journals included in the census a year ago but omitted from the present report, 10 are known to have ceased publication; and the same is very likely true of others from which no reply to our inquiries has been received.

New titles: Of the 58 publications added during the year, 34 are received by purchase; 3, by exchange; 21, gratis. Thirty-five of these are journals which have recently begun publication (1936–1939) and are now on file from the first number issued.

Number of separate issues received and filed: 14,748 (exclusive of duplicates, 6,223, and of reserves, 453). Of the total number, 2,131 were scattered issues received from Fellows and other donors; and 60 others were previously-lacking back-numbers supplied by publishers or editors in response to claims, completing 41 volumes.

Back files of 6 publications were purchased: 17 complete volumes.

The number of visitors to the Current-periodicals Room during the year was (approximately) 6,700—an increase of 200 over the number recorded for the preceding year. Of this year's total, some 1,300 were visitors during the 78 evenings the library was open.

Readers' Use of the Library

Library hours: the library was regularly open daily, except Sunday, from 9 to 6; on Wednesday and Friday evenings until 9:30. From June 12 to September 8, inclusive, the library was open Mondays to Fridays, inclusive, from 9 to 4, and closed on Saturdays and Sundays. The library was closed, as usual, on the following legal holidays: Thanksgiving, Christmas, New Year's, Memorial, Independence, and Labor days.

			Non-Fellows		*Fellows*		*Totals*	
	1939	*1938*	*1939*	*1938*	*1939*	*1938*	*1939*	*1938*
Number of visitors:								
Days	(293)	(294)	8,963	9,038	2,063	2,069	11,026	11,107
Evenings	(78)	(77)	1,516	1,288	204	217	1,720	1,505
			10,479	10,326	2,267	2,286	12,746	12,612

Circulation of books:	*1939*	*1938*
Number of volumes taken out	8,524	7,448
Number of volumes consulted in the library	49,725	49,038

The number of volumes "consulted in the library" includes only those supplied on demand. Readers have access to the bound volumes of periodicals and works of reference kept on the shelves in the Reading Room; the Fellows of the College, and occasionally others by special permission, have access to the book-stacks. There are, therefore, many volumes consulted of which no accurate record can be kept.

Inter-library loans: The library has sent 111 bound volumes on inter-library loan to 19 libraries, representing 11 States in the Union, and has borrowed on the same terms 21 volumes from 2 libraries. As happens each year, a number of requests for books on the restricted list had to be refused. In most of these cases the need was met by supplying photostatic copies of relevant parts of the book.

Use of the study rooms: Number of volumes used in these rooms during the year: 1,450 (1938: 576).

Photostat: 715 photostatic prints have been furnished to Fellows (1938: 312); 702 prints to non-Fellows (1938: 807); 1,274 prints to the library. The last include a copy of an incunabulum (bringing the total of photostated incunabula to 314), portraits, rare books on loan, etc.

Acquisitions and Accessions

Received from all sources:

1939: 3,992 volumes (including the bound and accessioned volumes of periodicals, 188 unbound reports and 1,383 duplicates); 2,792 pamphlets; 8,018 theses; 21,424 numbers of various journals.

1938: 2,524 volumes (including the bound and accessioned volumes of periodicals, 139 unbound reports and 343 duplicates); 4,570 pamphlets; 5,776 theses; 22,432 numbers of various journals.

Accessions:

1939: 2,421 volumes (1,136 by purchase; 824 by gift; 461 by exchange).
(Books, 1,050; Periodicals, 1,371).

1938: 2,042 volumes (1,050 by purchase; 641 by gift; 351 by exchange).
(Books, 678; Periodicals, 1,364).

Donations

The individual donors for the past year number 300 (1938: 310).

The library is indebted for large gifts of books, pamphlets and unbound periodicals to the following donors:

Dr. J. T. Bauer; P. Blakiston's Son & Co.; Drs. G. M. Boyd, C. W. Burr, Burton Chance, A. A. Eshner, J. B. Flick; Estate of Dr. J. H. Girvin; Mrs. Charles F. Griffith; Drs. S. McC. Hamill, Joseph Head, Bernard Kohn, E. B. Krumbhaar, M. A. Lindauer; Medical Library Association Exchange; Drs. A. C. Morgan, F. D. Patterson; Philadelphia City Institute Library; Drs. David Riesman, P. J. Sartain; W. B. Saunders Co.; Bequest of Dr. G. E. de Schweinitz; Drs. E. A. Shumway, S. R. Skillern, J. M. Thorington; University of Pennsylvania Library; Drs. Joseph Walsh, G. B. Wood.

Various publishing houses have presented volumes as follows: P. Blakiston's Son & Co., 9; F. A. Davis Co., 22; Lea and Febiger, 22; J. B. Lippincott Co., 8; W. B. Saunders Co., 233 (not all new publications).

Thirty-one volumes were presented by the following authors or editors: A. Benchetrit, W. R. Bett, G. D. Biven, W. Boyd, H. A. Christian, W. B. Davis, P. Findley, S. Flexner, H. Fox, A. Gordon, R. T. Gunther, G. Hinsdale, D. R. Iriarte, C. Jackson and C. L. Jackson, A. J. Lanza, L. B. London, J. McFarland, V. H. Moon, J. H. Musser, E. Pasquier, W. A. Pearson, J. L. Rice, D. Riesman, M. von Rohr, R. H. Shryock, H. Silvette, R. Simon, L. E. Snodgrass, G. C. Terry, G. H. Wahmann.

Exchanges

The *Transactions & Studies* was sent, either as gift or in exchange for 293 other serial publications, to 328 organizations.

Ninety distributions of books or journals (1 volume and 1,407 unbound journals) have been made through the Medical Library Association Exchange. The library has received thirty-four such distributions.

Theses and dissertations to the number of 3,333 have been received from the following European Schools of Medicine with which we exchange publications at the present time: Universities of Amsterdam, Basel, Berlin, Bern, Bonn, Breslau, Copenhagen, Erlangen, Geneva, Giessen, Göttingen, Greifswald, Halle, Heidelberg, Jena, Kiel, Köln, Königsberg, Lausanne, Leiden, Liège, Marburg, Paris, Rostock, Tübingen, Würzburg.

Work of the Cataloguers

	1939	*1938*
Number of works classified, shelf-listed, and for which cards were filed	929	1,136
Cards typewritten, examined, and filed	8,647	6,379
Other cards altered and filed	10,341	8,638
Pamphlets and reprints subject-headed and arranged alphabetically by subject, and by author under the subject	1,825	2,790

Miscellaneous Activities

Exhibits. A memorial exhibit of the published works of Dr. Sigmund Freud was presented a few days after the author's death. Other extensive exhibits were devoted to the subjects of endocrinology, anemia, allergy, and to works illustrating the major advances in the history of surgery. Following our custom, a special exhibit was prepared for each of the meetings of the Section on Medical History. There can be no doubt, if one may judge from many comments, that these exhibits contribute materially to a better general knowledge of the library's resources and to the development of a historical perspective, in both our readers and ourselves.

Projects Undertaken. The Union List of Serials is, as most of our readers know, a mammoth and invaluable volume containing not only the names of practically all the serial publications that are held by the major American libraries, but, also, indications as to which volumes may be found in each of the libraries. Our library is not represented in the first edition of the Union List, an omission which has brought expressions of surprise and regret from many libraries and individual scholars. These will be pleased to know that the Library Committee has agreed to the inclusion of the library's holdings in the new edition, and that the arduous task of checking has been under way for several months.

After careful consideration, the Library Committee adopted a

proposal, made by a member of the Committee, that the subject cards in the catalogue be so divided, in the larger classifications, as to indicate at a glance the works published before 1900 and those published after 1899. This division is being carried out gradually by a member of the staff, and it is believed that it will facilitate the use of the catalogue by those interested only in the works of relatively modern date.

Through the generosity of the library's farsighted friend Dr. Charles W. Burr, the library has acquired an Argus microfilm reader. The Bibliofilm Service in Washington is prepared to supply, at very reasonable cost, a microfilm copy of any work in the Army Medical Library, the Library of Congress, and other great libraries. The need for borrowing volumes on interlibrary loan is thereby greatly reduced, to the advantage of the lending library, and readers are enabled to consult material which would not be sent on loan in its original form under any conditions. Though still in its infancy, the production of written material on microfilm bids fair, we believe, to become the greatest single aid to scholarly research since the invention of printing with movable type.

The Staff. The librarian read a paper at the annual meeting of the American Association of the History of Medicine (published in the July, 1939, issue of the *Bulletin of the History of Medicine*); was guest-speaker at the patron's annual dinner to the members of a local undergraduate medical society; contributed a brief piece to the March, 1939, number of the *Annals of Medical History*, and another to the February, 1939, number of the College's *Transactions & Studies;* attended, at Newark, in June, a meeting of the Executive Committee of the Medical Library Association; continued as editor of the *Transactions & Studies.*

The staff of assistants, unchanged in membership throughout the year, comprised the following: Miss Gertrude Bishop, cataloguer; Miss Sallie H. Todd, assistant cataloguer; Miss Helen Jackson, assistant in charge of the Reading Room; Mr. R. H. Baugh, assistant in charge of the Current-periodicals Room; Miss Kathryn Haegele, junior assistant, and substitute assistant in charge of the Reading Room; Miss Marion Jackson, junior

assistant and photostat operator; Miss Hertha Bishop, junior assistant in charge of book-orders; Mrs. H. C. Wood, 3d., part-time assistant, on assignment chiefly in the Current-periodicals Room.

W. B. McDaniel, 2d,
Librarian.

Approved:
David Riesman, M.D.,
Chairman

Report of the Committee on the Mütter Museum

The Museum was open, on days when the College building was open, from 10 to 1, and from 2 to 6, except Saturdays, when the hours were 9 to 1. During these hours the clerk-technician was constantly in attendance, and the curator was often present, also. In addition, the Museum was open on the evenings of the Stated Meetings of the College, the clerk-technician being in attendance. At the request of some of the Sections of the College, the Museum was opened for an hour or so before certain of their meetings. The clerk-technician reports a considerable increase in the number of visitors during the year.

The Thomas Dent Mütter Lecture LI was given by Dr. William Boyd, of the University of Toronto, who spoke on "Some Reasons for the Recent Increase of Bronchial Carcinoma."*

Further study of the Museum's giant skeleton (see the curator's article on it in the *Transactions & Studies*, September, 1938) is being undertaken by Dr. Charles D. Humberd, an authority on giantism. Calling attention to the skeleton as "the largest and most spectacular that can be seen in America," Dr. Humberd has published (*Kentucky Med. J.*, February, 1939, p. 82) a request for information as to the identity and life history of the subject.

A bottle containing a specimen of opium was deposited in the Mütter Museum in 1853 by Dr. Charles D. Meigs, with directions that the bottle should not be opened for fifty years. The specimen remained unstudied until 1939, when at the request of the Mütter Museum Committee and the curator, Dr. Horatio C. Wood, Jr., and Professor Arthur Osol, of the Philadelphia College of Pharmacy, made an assay of the specimen. With the acquiescence of the Mütter Museum Committee, and properly crediting the Mütter Museum of the College, Dr. Wood and Professor Osol published a report of their findings in the *American Journal of Pharmacy*, October, 1939, pp. 380–384. These may be sum-

* Printed in the *Transactions & Studies*, 4th ser., vol. 6, no. 4, pp. 317–328, February, 1939.

marized by quoting the following paragraph, contained in a letter directed by Professor Osol to the Mütter Museum Committee:

> The one conclusion which I can draw is that morphine, as present in opium, is substantially stable over a period of 86 years. However, it is not possible to say whether there has been any change, for the label of the container states that the sample of opium contained 10 per cent of morphine—but no assay method is indicated. As the results of different assays are known to vary appreciably, it would be erroneous to say that there has or has not been any change. But we may say that the change, if any, has not been very great.

The Peter A. Browne Collection of Hair in the Mütter Museum served as the basis of an interesting and instructive paper on "A Resurrection of 'Pile' " by Dr. Joseph McFarland, curator of the Mütter Museum.*

During the past year, several exhibits were re-arranged with especial reference to the several diseases, leading to a better grouping and making the exhibits more available for observation and study. The assemblage of all specimens of tumors was completed during the year.

Accessions to the permanent collection of the Museum and subject to the Mütter Deed of Gift were as follows:

Stethoscope, formerly belonging to John Wilson Johnston, M.D. Presented by A. C. Morgan, M.D.

Cast of the left hand of a 232 cm. giant of the infantilism type. Presented by Charles D. Humberd, M.D.

First pair of cemented bifocals, made on the prescription of Dr. George M. Gould by Wall & Ochs, in 1888, for Dr. Oliver P. Rex. Presented by the estate of Laura Stedman Gould Dees.

The Matthew H. Cryer, M.D., Anatomical Collection. This consists of a large number of dissections of the face, teeth, and jaws. Presented as a permanent gift by Mrs. Cryer.

Dr. Joseph McFarland was re-appointed curator of the Museum for the year 1939–1940, and Mrs. Ella N. Wade was appointed clerk-technician as of October 1, 1939, replacing Miss Janet Higgins, resigned.

J. Parsons Schaeffer, M.D.,
Chairman.

* Printed in the *Transactions & Studies*, 4th ser., vol. 7, no. 3, pp. 278–296, December, 1939.

Report of the Committee on College Collections

In accord with the appropriation available for the purpose, the Committee continued its interest in the renovation of the College's oil portraits. Those of Oliver Wendell Holmes, James H. Hutchinson, William Shippen, Alfred Stillé, and William Thomson were renovated by Justin Pardi.

During the year the curator and the clerk-technician began the making of a new catalogue covering all the collections under the care of the Committee. It is hoped that the catalogue may be completed during the coming fiscal year.

Descriptive lists of the accessions for the year may be found in the June and December, 1939, numbers, pp. 210 and 299, respectively, of the *Transactions & Studies*.

Dr. Joseph McFarland was re-appointed curator of the College Collections for the year 1939–1940, and Mrs. Ella N. Wade was appointed clerk-technician as of October 1, 1939, replacing Miss Janet Higgins, resigned.

J. Parsons Schaeffer, M.D.,
Chairman.

Reports of the Treasurer for the Year Ended November 30, 1939

BALANCE SHEET

Assets			
Plant			
Land at 22d & Ludlow Sts.	$46,409.75		
Building at this address	364,681.41	$411,091.16	
Other Real Estate			
Land at 13th & Locust Sts.		150,000.00	
Fund Investments			
Stocks, Bonds, Mortgages and Real Estate			
Received in Foreclosure		685,493.15	
Income Invested in Bonds		3,955.00	
Accounts Receivable		239.28	
Notes Receivable		500.00	
Cash			
Trust Funds			
Principal Account for Investment	2.63		
Income	8,373.19		
Administration	5,644.58	14,020.40	
Total			$1,265,298.99
Liabilities			
Unexpended Appropriations			
Library General Account	1,837.98		
Publication Committee	339.20		
Contributions for Furnishing President's Room	525.00		
			2,702.18
			$1,262,596.81
Plant Funds Invested in Land and Building		$561,091.16	
College Funds			
Library Funds	$440,708.92		
Publication Funds	15,898.73		
Prize and Lecture Funds	30,571.32		
General Operating Funds	178,470.17		
Entertainment Funds	12,020.62		
Miscellaneous Funds	9,814.29	687,484.05	
Income from Special Funds Invested		3,955.00	
Unexpended Income from Funds for Special Purposes		8,373.19	
Unexpended Current Operating Income		1,693.41	
			$1,262,596.81

CASH STATEMENT, NOVEMBER 30, 1939

Receipts		
Balance on hand 12–1–38		$11,851.68
Bequests		
Carolyn Tyler & Arthur H. Lea	50,000.00	
Samuel Clarkson	3,000.00	
Charles H. Vinton (Bal. of Est.)	236.26	53,236.26
Investments matured or sold		51,001.32
Accretions to Principal from sale of above securities		7,850.88
Income transferred to Principal		100.00
Pledges paid to Reserve Fund		20.00
Entrance Contribution to Reserve Fund		730.00
Contributions from Fellows		18,704.00
Contributions for use of Halls		1,207.50
Contributions for use of Lantern		253.00
Contribution to Committee on College Collections for Portrait Renovation		208.76
Rent from Property 13th & Locust Sts.		7,125.00
Dividends from Insurance		137.50
Interest on Western Savings Account		81.00
Interest on Notes Receivable		16.34
Notes Receivable		200.00
Income from Special Funds		28,471.36
Income from Library		1,739.20
Miscellaneous Income		113.62
Total		$183,047.42
Less Total Disbursements		169,027.02
Balance on hand November 30, 1939		$14,020.40

Disbursements	
Securities Purchased	$112,872.28
Committee on College Collections	869.23
Hall Committee	10,121.81
Committee on Publication	2,195.96
Secretary	2,315.90
Treasurer	9,908.89
Library Committee	26,110.69
Friends of Library	108.68
Notes Receivable	700.00
Miscellaneous Disbursements	3,823.58
	$169,027.02

Penna. Company Principal Account	2.63	Principal Account for Investment 2.63
Penna. Company Income Account	11,062.06	Trust Fund Income Account 8,373.19
Western Savings Fund Account	2,933.29	Administration 5,644.58
Petty Cash Account	22.42	
Total Cash Balance	$14,020.40	Total $14,020.40

SUMMARY OF OPERATING INCOME AND EXPENDITURES, 1939

Balance on hand 12-1-38		$542.27	
Income			
Contributions from Fellows	$18,704.00		
Contributions for use of Halls	1,207.50		
Contributions for use of Lantern	253.00		
Contribution to Committee on College Collections for Portrait Renovation	208.76		
Rent Property 13th & Locust Sts	7,125.00		
Insurance Dividends	137.50		
Interest on Western Savings Fund Account	81.00		
Income from Funds for General Operating Purposes	6,114.32	33,831.08	
Total			$34,373.35
Expenditures			
Hall Committee		10,119.39	
Library Committee		8,200.00	
Treasurer		9,885.32	
Secretary		2,306.00	
Publication Committee		1,300.00	
Committee on College Collections		869.23	
			32,679.94
Unexpended Operating Income			$1,693.41

SUMMARY OF COLLEGE TRUST FUNDS

	Principal	*Investment*	*Balance of Income (1938)*	*Income*	*Expenditures*	*Balance of Income (1939)*
Library Funds	$440,708.92	$440,106.13	$2,082.10	$18,914.45	$18,864.62	$2,131.93
Publication Funds	15,898.73	15,836.34		658.52	658.52	
Prize and Lectureship Funds	30,571.32	30,522.61	3,425.66	1,054.48	1,100.45	3,379.69
General Operating Funds	178,470.17	177,928.99		6,989.50	7,047.05	(57.55)
Entertainment Funds	12,020.62	11,982.05	(1,099.32)	437.25	174.99	(837.06)
Miscellaneous Funds	9,814.29	9,747.03	3,322.68	433.50		3,756.18
	$687,484.05	$685,493.15	$7,731.12	$28,487.70	$27,845.63	$8,373.19

	Principal	*Investment*	*Balance of Income (1938)*	*Income*	*Expenditures*	*Balance of Income (1939)*
Library Funds						
Baker, Henrietta R. F.	$5,412.06	$5,378.61	$47.20	$265.00	$290.41	$21.79
Bent, Luther S.	1,003.75	963.25	24.62	45.00	57.61	12.01
Binding Books, Periodicals, etc.	420.00	400.00		21.17	21.17	
Carter, Wm. T.	5,000.00	4,966.88	80.98	157.50	155.27	83.21
Catalogue Endowment	1,030.32	1,024.35		31.50	31.50	
Clarkson, Gerardus	1,000.00	967.50	27.53	10.00	26.70	10.83
Dercum, Francis X.	5,000.00	4,993.50	72.44	144.50	125.92	91.02
Duhring, Louis A. (Book)	5,006.25	4,998.81	136.94	218.75	223.57	132.12
Duhring, Louis A. (Library)	267,027.44	266,863.54		11,850.90	11,850.90	
Eshner, Augustus A.	5,000.00	5,000.00	68.30	300.00	237.13	131.17
Friends of Library #2	361.29	360.00	23.10	3.00		26.10
Griscom, John D.	3,250.00	3,337.50	31.52	250.00	207.82	73.70
Harte, Richard H.	5,169.30	5,185.87	169.56	173.02	267.39	75.19
Hunter, Charles T.	489.73	454.19	3.43	3.00		6.43
Rare Book	475.00	451.20	38.00	19.00		57.00
Jenks, William F.	7,026.56	7,050.25	(11.87)	257.78	135.99	109.92
Judson, Oliver A.	1,139.91	1,138.84	10.53	50.45	47.07	13.91
Keating, Wm. V. and John M.	1,003.75	953.88	15.10	45.00	38.18	21.92
Keen, William W.	5,435.18	5,404.10	66.21	202.34	218.92	49.63
Leffman, Henry			199.78	394.52	464.40	147.90

Library Endowment	14,787.75	14,799.99	118.95	271.76	327.15	63.56
Longstreth, Morris	23,673.45	23,637.68		837.38	837.38	
Magee, Horace	15,146.06	15,129.94	29.89	515.66	484.15	61.40
Mears, J. Ewing	5,411.87	5,392.80	5.19	258.00	249.82	13.37
Mills, Charles K.	182.71	161.30	1.83	2.00		3.83
Mitchell, S. Weir	5,140.00	5,119.64	44.10	233.95	177.80	100.25
Montgomery, E. E.	3,220.85	3,207.82	91.96	167.06	234.48	24.54
Musser, John H.	518.59	500.00	13.38	22.50	20.96	14.92
Newcomet, Elizabeth K.			25.05	71.25	23.90	72.40
Norris, William F.	4,593.07	4,621.89	32.29	195.01	188.87	38.43
Oliver, Charles A., Memorial	1,270.65	1,222.45	69.48	55.54	124.94	.08
Phila. Medical Society	557.50	570.25	15.92	27.00	17.68	25.24
Rodman, Lewis	5,074.64	5,080.26	40.15	153.94	156.61	37.48
Vinton, Charles H.	11,337.22	11,279.20	108.85	641.14	517.14	232.85
Warren, Douglas Stockton	3,000.00	3,009.00	70.29	124.00	138.43	55.86
Weightman, John F.	1,072.50	1,067.64	74.91	49.70	118.76	5.85
White, J. William	5,240.91	5,210.13	105.61	251.00	215.72	140.89
Wistar, Caspar	5,263.53	5,242.02	57.47	186.27	188.22	55.52
Wood, George B.	9,967.08	9,980.35	168.38	408.86	456.61	120.63
Ziegler, S. Lewis	5,000.00	4,981.50	5.03		4.05	.98
	$440,708.92	$440,106.13	$2,082.10	$18,914.45	$18,864.62	$2,131.93

	Principal	*Investment*	*Balance of Income (1938)*	*Income*	*Expenditures*	*Balance of Income (1939)*
Publication Funds						
Da Costa, J. M.	$4,766.05	$4,801.84		$188.76	$188.76	
Davis, G. G.	491.87	491.87		22.50	22.50	
General Publication	2,067.54	2,068.84		93.95	93.95	
Lister International Medical Congress	2,009.78	1,976.75		50.86	50.86	
Meigs, Arthur V.	1,034.50	1,000.00		50.00	50.00	
Tyson, James	528.99	498.50		22.50	22.50	
Wyeth, Francis Houston	5,000.00	4,998.54		229.95	229.95	
	$15,898.73	$15,836.34		$658.52	$658.52	
Prize and Lectureship Funds						
Alvarenga Prize	$9,568.33	$9,523.82	$1,049.24	$272.48	$312.15	$1,009.57
Anders, James M., Lectureship Fund	6,002.99	5,993.79	884.19	292.00	94.30	1,081.89
Newbold, Mary Scott, Lectureship Fund	15,000.00	15,005.00	1,492.23	490.00	694.00	1,288.23
	$30,571.32	$30,522.61	$3,425.66	$1,054.48	$1,100.45	$3,379.69
General Operating Funds						
Clarkson, Samuel	$3,000.00	$3,011.61			$57.55	($57.55)
College Endowment	14,817.92	14,834.24		707.58	707.58	
Lea, Carolyn Tyler and Arthur H	50,000.00	50,033.50		1,605.00	1,605.00	
Reserve	53,616.58	52,272.53		1,587.26	1,587.26	
Shippen, Elizabeth	5,109.73	5,107.73		281.19	281.19	
Weightman, William, Memorial	51,925.94	52,039.38		2,808.47	2,808.47	
	$178,470.17	$177,298.99		$6,989.50	$7,047.05	($57.55)
Entertainment Funds						
Harte, Richard H.	$4,690.57	$4,666.01	($1,972.90)	$358.97	$174.99	($1,788.92)
Mitchell, S. Weir	7,330.05	7,316.04	873.58	78.28		951.86
	$12,020.62	$11,982.05	($1,099.32)	$437.25	$174.99	($837.06)
Miscellaneous Funds						
Abbe, Robert	$5,740.19	$5,737.09	$1,853.80	$379.50		$2,233.30
Gross, Samuel D.	2,910.00	2,859.75	630.13			630.13
Wood, Horatio C.	1,164.10	1,150.19	838.75	54.00		892.75
	$9,814.29	$9,747.03	$3,322.68	$433.50		$3,756.18

T. Grier Miller, M.D.
Treasurer

Report of the Women's Committee on the Sinkler Garden

In a paper read before the College in 1787, Dr. Benjamin Rush, setting forth proper objectives for the College, proposed the formation of a medical library and the development of an herb garden. The first was started almost immediately and today is in the front rank of medical libraries. However, not until the College had moved into its fifth and present home did it acquire the long-projected garden.

In 1911, the lot adjoining the College, and lying between it and the Church of the New Jerusalem Society of Philadelphia, was purchased by Mr. Eckley Coxe and conveyed as a gift to the College, with the understanding that it should be a memorial of some kind to his uncle, Dr. Wharton Sinkler. A flower garden was decided upon and the Sinkler Memorial Garden was planned and planted. Owing to lack of funds and drainage problems, the garden did not thrive.

In the spring of 1937, when the College was about to celebrate its 150th anniversary, it was decided to convert the garden into one of medicinal herbs, as Dr. Rush had suggested so many years ago. This was done with the help of the Weeders Garden Club and with contributions from wives of the Fellows. The Philadelphia Unit of the Herb Society of America was asked to co-operate, and it has taken over the supervision of this project.

Experience proved in a year or so that little of value could be accomplished until certain problems of grading and drainage were faced and met. We were fortunate in interesting Mr. John P. B. Sinkler, who very kindly donated his time and experience to studying these problems. On his advice, a brick retaining-wall was built on the south side of the garden, running the length of the Church on the party line between the Church and the College. The Church was most interested and co-operative, and very generously contributed $230 towards the project, thus materially

supplementing a loan made by the College to the committee in charge of replanting the garden.

A history of the garden and an appeal were sent out to those who might be interested, and a Society called the "Friends of the Garden" was formed, composed of wives of Fellows of the College, with annual dues of $1. In addition, the central Committee of the Herb Society of America, in Boston, contributed $100.

After the retaining-wall was built, all old plants were taken out, new soil was put in, the ground manured and fertilized, a large number of trees, bushes and shrubs planted on the property, and a hedge planted all around the garden. A re-arrangement of medicinal herbs was made, a new planting set out, and a large number of bulbs has been put in for next spring. As the purpose is to make the garden an educational, as well as an ornamental, feature of the College, the herbs will all be labeled and a chart made of their arrangement. The Committee hopes to stimulate interest among the "Friends of the Garden" by having a garden party or plant sale in the garden next spring.

There are infinite possibilities for both interest and beauty in the garden, and we hope that the Fellows and their wives will feel, with us, desirous of making its future permanent and secure.

The Garden Committee

Mrs. John H. Gibbon
Miss Edith Stokes Haines
Mrs. Walter Rebmann
Mrs. Alfred Stengel
Mrs. Robert G. Torrey
Mrs. Pierce Archer

Index to Volume 7

Abell, Richard G., 173
Addison, W. H. F., 57
Adler, Francis H., 351
Allbritten, F. F., 349
Anders Lecture (Dyer), 232
Anemia, diagnosis and treatment of (Castle), 129
Angina pectoris, etiology and treatment of (Kerr), 162
Arsphenamine and neo-arsphenamine, treponemacidal activity of in vitro (abstract), 47
Arthritis, hypertrophic, origin and nature of (Bauer), 1
Austin, J. Harold, 59
Baer, B. F., Jr., memoir of, 198
Barnshaw, Harold D., 262
Batson, Oscar V., 351
Bauer, Walter, 1
Beck, Claude S., 211
Behrend, Moses, 63
Belk, William P., 260
Bernstein, Mitchell, 172
Bielschowsky, Alfred, 62
Blalock, Alfred, 345
Bond, Earl D., 171
Borzell, Francis F., 263
Browne, P. A., collection of "pile" (McFarland), 278
Burns, Louis J., 63
Burns, Michael, memoir of, 120
Campbell, Edward H., 62
Carrara, J. M. A., Medico-mnemonic treatise of (McDaniel), 353
Castiglioni, Arturo, 264
Castle, W. B., 129
Chance, Burton, 172, 173, 351
Church, Franklin H., 262
Clark, Eleanor Linton, 173
Clark, Eliot R., 173
Clinical teaching in America (Riesman), 89
Cohen, J. Gershon-, 172
Cohen, Samuel, 351
College Collections, Report of committee on, 398; See also under College Notes, 210, 299
College Notes, 121, 205, 297
Committees, membership of, 124
Cowan, Alfred, 62
Currents and counter-currents in medical progress (Stengel), 64
Cutler, J. W., 171
Cuttle, Tracy D., 54
Dandy, Walter E., 263
Davis, Warren B., 351
Diabetes mellitus (Long), 21
Dihydrotachysterol in parathyroid deficiency (abstract), 51
Diller, Theodore, 262
Donnelly, Joseph C., 351
Duncan, Garfield G., 54
Dunn, C. W., 260
Dunnington, John H., 173
Dyer, R. E., 232
Edwards, Joseph C., 50
Ellis, Van M., 62 (bis)
Epileptics, treatment of by sodium diphenyl hydantoinate, 52
Evans, Everett, 54
Farmer, Harold, 262
Feldman, Jacob B., 173
Flick, Lawrence F., memoir of, 114
Flippin, Harrison F., 56, 171
Freeman, Joseph T., 348
Friends of the Library, 350 *n* 13
Gibson, Glen G., 49, 173
Girvin, John H., memoir of, 111

Grazier, Clark G., 350
Griffith, John Q., Jr., 261
Gross, Elmer R., 263
Hair, see under Pile
Harvey, Ethel Browne, 60
Hatfield, Charles J., 173
Hatfield Lectures: Bauer, 1; Long, 21
Haverhillia multiformis septicemia (abstract), 349
Heart, surgical approach to diseases of (Beck), 211
Henry, Norman W., 260
Hewson, Addinell, memoir of, 192
Hewson, William, 351
Hitchens, A. Parker, 172
Hodes, Philip J., 261
Hughson, Walter, 351
Hussey, Raymond, 49
Hypertension, essential, correlation study of (abstract), 49
Hypotension, orthostatic, observations on (abstract), 347
Igersheimer, Josef, 262
Irradiation sickness (abstract), 348
Ivy, Robert H., 263, 351
Jackson, Chevalier L., 351
Jacobs, Maurice S., 171, 175
Jeffers, William A., 349
Karsner, Howard T., 301
Kast, Clara C., 47
Kerr, William J., 162
Klauder, Joseph V., 263
Kolmer, John A., 47, 350
Kornblum, Karl, 62, 348
Krumbhaar, E. B., 58, 189
Langdon, H. Maxwell, 62, 263
Laplace, Louis B., 347
Leaman, William J., 172
Lectures, list of (1939): public, 346; scientific, 345
Lectureship committees, 125
Lehrfeld, Louis, 62
Lewy, F. H., 62
Library Committee, Report of, 381; see also under College Notes, 207, 298
Long, C. N. H., 21
McDaniel, W. B., 2d, 353
McDonald, Robb, 351
Macfarlan, Douglas, 173
McFarland, Joseph, 278
McNair, Stirling S., 173
Medicine, preventive, in Bible and Talmud (Jacobs), 175
Mengel, Willard G., 173
Miller, Jerome, 62
Molitor, Hans, 350
Moon, Virgil H., 348
Morgan, David R., 348
Morrison, Lester M., 172
Mütter Lecture (Karsner), 301
Mütter Museum, Report of committee on, 396; see also under College Notes, 209
Muller, George P., 171; (President's address), 369
Naide, Meyer, 171
Newbold Lectures: Castle, 129; Kerr, 162; Beck, 211; Blalock (title), 345
Newmayer, S. Weir, 173
Officers and committees, 124
Ovarian tumors associated with sexual endocrine dysfunction (Karsner), 301
Packard, Francis R., 111
Palmer, C. L., 263
Parathyroid deficiency, effect of dihydrotachysterol in (abstract), 51
Parker, Walter R., 351
Pennsylvania Hospital, Sulfapyridine in use at (abstract), 54
Pepper, D. Sergeant, 55
Pepper, O. H. Perry, 346
Periarteritis nodosa (abstract), 53
Peterson, Charles W., 47

Philadelphia General Hospital, mortality of pneumonococcic pneumonia (abstract), 56
Piersol, George Morris, 62, 198
Pile, P. A. Browne collection of (McFarland), 278
Pneumonia, pneumococcic, mortality of at Phila. Gen. Hosp. (abstract), 56
President's address (Muller), 369
Preventive medicine in Bible and Talmud (Jacobs), 175
Prize committees and trustees, 125
Public Lectures, list of, 346
Read, Hilton S., 173
Read, W. T., Jr., 262
Respiratory infection, epidemic, experiments in environmental control of (W. F. Wells et al.), 342
Rickettsioses of N. America (Dyer), 232
Riesman, David, 89
Robertson, Harold F., 263
Roesler, Hugo, 49
Rome, legacy of to history of medicine (Castiglioni), 264
Rose, Edward, 51
Rowntree, L. G., 261
Scarf, Maxwell, 53
Schaeffer, J. Parsons, 192
Scheie, Harold G., 62
Schenck, Harry P., 173
Schmidt, Carl F., 350
Schwartz, Leon, 56
Scott, Kenneth S., 52
Sections, officers of, 126
Sections, programs and abstracts of: General Medicine, 47, 171, 260, 347; Medical History, 57, 172, 262, 350; Ophthalmology, 61, 173, 262, 351; Otolaryngology, 62, 173, 263, 351; Public Health, 62, 174, 263, 352
Shay, Harry, 172
Sheely, R. F., 349
Shumway, Edward A., 61
Simkins, Samuel, 172
Sinkler Garden, Report of Women's Committee on, 405
Smith, Austin T., 62
Sodium diphenyl hydantoinate in treatment of epileptics (abstract), 52
Souders, Benjamin, 351
Spaeth, Edmund B., 263
Squill, see Urginin
Stengel, Alfred, 64
Stokes, Joseph, Jr., 342
Strecker, Edward A., 120
Stroud, William D., 50
Sudhoff, Karl, memoir of, 189
Sulfapyridine, experience with at Pa. Hosp. (abstract), 54; in pneumococcic and gonococcic infections (abstract), 55
Sunderman, F. William, 51
Temkin, Owsei, 172
Thorner, Melvin W., 351
Trasoff, Abraham, 53
Treasurer's Report, 399
Urginin, clinical use of (abstract), 50
Vaccaro, Leopold, 172
Vander Veer, Joseph B., 50
Vitamin deficiency with reference to certain disease states (abstract), 348
Walsh, Joseph, 114
Wells, Mildred W., 342
Wells, W. F., 342
Wilder, Theodore S., 342
Wilson, George, 52
Wirts, C. W., Jr., 172
Wohl, Michael G., 348
Women's committee on Sinkler Garden, report of, 405
Yaskin, Joseph C., 174

TRANSACTIONS
& STUDIES
of the
College of Physicians
of
Philadelphia

FOURTH SERIES

VOLUME 7

NUMBER 1

PUBLISHED AT BALTIMORE, MARYLAND

April, 1939

INDEX NUMBER

TRANSACTIONS & STUDIES *of the* College of Physicians *of* Philadelphia

FOURTH SERIES

VOLUME 7
NUMBER 4

PUBLISHED AT BALTIMORE, MARYLAND
February, 1940

College of Physicians of Philadelphia

Instituted 1787

1940

President
E. B. Krumbhaar

Vice-President
O. H. Perry Pepper

Censors
John H. Gibbon
Albert P. Brubaker
Francis R. Packard
Charles W. Burr

Secretary
J. Harold Austin

Treasurer
John B. Flick

Honorary Librarian
David Riesman

Ex-Presidential Councillor
George P. Muller

Elective Councillors
E. J. G. Beardsley
Edward B. Hodge
Eugene P. Pendergrass
Truman G. Schnabel
Robert H. Ivy
T. Grier Miller

Council
The Foregoing Officers and the Chairmen of the Nine Standing Committees

---

Librarian
W. B. McDaniel, 2d

Curator of the Mütter Museum
Joseph McFarland

Committee on Publication
W. Osler Abbott, *Chairman*
Thomas Fitz-Hugh, Jr.
John H. Gibbon, Jr.

Editor of the *Transactions & Studies*
W. B. McDaniel, 2d